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AEROSOL THERAPY OF RESPIRATORY DISEASE

A Report of Fifty Cases

VERNON BRYSON, PH.D.,* AND EDWIN J. GRACE, M.D.†

COLD SPRING HARBOR AND BROOKLYN, NEW YORK

AEROSOL therapy may be defined as the medicinal administration of fine solid particles or liquid mists as inhalants. The method has never been widely used in the treatment of disease, although asthmatic patients have been given symptomatic relief with epinephrine aerosols for many years. To anyone familiar with the basic studies on the subject,[1–7] the administration of antibiotics as aerosols appears to be a logical and necessary development. It may be anticipated that the advantages of simple administration and a relatively constant rate of absorption will eventually induce medical investigators to explore more fully the process of aerosolization as a technic for giving antibiotics, chemotherapeutic agents, enzymes, antibodies, endocrines, radiologically opaque solutions, bacteriophage, radioactive isotopes and many other diverse chemical materials.

From early in the war until recently, one of us (V. B.) was engaged in research‡ on the physical and biologic properties of aerosols for the Technical Division, Office of the Chief, Chemical Warfare Service.[8] Publication in 1944 of a report on the production of penicillin aerosols and their inhalation by animals and man stimulated the interest of clinicians in the application of antibiotic mists for the treatment of pulmonary infection.[9] Further studies were pursued for the Technical Division on a co-operative basis with the College of Physicians and Surgeons of Columbia University and later under contract to the Medical Division, Chemical Warfare Service. In addition, we have carried on an independent program resulting in the accumulation of clinical data on the use of aerosols in the treatment of respiratory infection. This work is reported below.

Considerable knowledge has been gained recently on the clinical application of penicillin aerosols, notably by Olsen,[10] Barach et al.,[11] Vermilye,[12] Segal and Ryder,[13] Humphrey and Joules[14] and by Southwell.[15] It is now known that blood levels well above the minimum bacteriostatic requirement to inhibit the growth of nonresistant staphylococci and streptococci can easily be obtained.[11] The presence of penicillin in the blood and urine after penicillin aerosol therapy may justifiably be regarded as proof that the antibiotic is being absorbed.[9] The attainment of high blood levels at the expense of unduly complex rebreathing apparatus and accessory equipment, however, does not seem to us a warranted procedure, except when demonstrably more effective clinically. Segal and Ryder[13] have obtained striking clinical improvement in 2 cases in which no blood level could be demonstrated after aerosol therapy. Their conclusions that blood levels are mainly of academic interest rather than practical value and that the clinical course of a disease should be the criterion of effective treatment are probably justified.

At the present time a trend to the use of increasingly complex accessory equipment in the production and administration of therapeutic aerosols is apparent.[16, 17] The value of complex baffles, valves and rebreathing devices is problematical. Actually, all that is needed to administer aerosol therapy is a suitable nebulizer,§ a source of compressed air or oxygen and a rubber tube. Insertion of a Y tube or small hole in the tubing connecting the oxygen tank and nebulizer enables the patient to operate the nebulizer only during inhalation by placing his finger over the open end of the Y tube or hole in the rubber tube.[11, 18] A small electrically motivated air compressor may be used as a substitute for tank oxygen, provided that the air is carefully filtered to remove any machine oil and that supplementary oxygen is not required.[14]

At the outset we were convinced that if penicillin aerosol therapy was to be a generally useful thera-

*Research biologist, Long Island Biological Society, Cold Spring Harbor, New York.

†Clinical director, Huntington Hospital; associate attending physician, St. John's and Brooklyn hospitals.

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§Vaponefrin — obtainable from Vaponefrin Company, Upper Darby, Pennsylvania — or DeVilbiss 40 — obtainable from DeVilbiss Company, 111 Eighth Avenue, New York City.

peutic method, simplicity of equipment and procedure was vital. By means of a nebulizer (for which the ordinary unbaffled atomizer is not a substitute), the patient inhales aerosolized penicillin either through cannulae passing into the nose or by mouth, depending on the clinical problem involved. When possible, deep inspiration on the part of the patient aids in the maximum distribution and retention of aerosol. Our subsequent experience, as well as that of Olsen[10] at the Mayo Clinic, has demonstrated the value of a simple technic.

At the same time it is necessary to select the necessary minimum of equipment with care. Experimental evidence indicates that to penetrate to the smaller bronchioles and alveoli of the lungs, aerosols must be composed of small particles, on the order of magnitude of 5 microns in diameter or less.[19] Large particles are impinged by convection in the nose, throat and upper respiratory passages and are undesirable, except for the treatment of infectious tracheitis, laryngitis and other diseases of the larger respiratory passages or for mucosography.[20] Therefore, the clinician must distinguish between the ordinary commercial atomizer, which produces relatively large droplets on the principle of a flit gun, and the nebulizer. A nebulizer is constructed with some intermediate baffle interposed between the spray jet and the orifice; larger particles impinging on this baffle are broken into smaller droplets and expelled, or returned by gravitational force to the main reservoir for recirculation. Even some commercial nebulizers produce a considerable percentage of large particles, which merely means that a greater proportion of the inhaled solution is delivered to the surface of the throat, larynx and trachea. The treatment of respiratory disease may, in fact, be accomplished by an ordinary atomizer, as reported by Morse.[21] In this event the principal effect on alveolar or bronchiolar surfaces is achieved topically by the fraction of small particles present in an atomized spray, together with an indirect systemic action of material absorbed from epithelial surfaces of the upper respiratory tract. The method is suitable for nontoxic substances, but if Promin[22, 23] or similar materials are to be used further for topical aerosol therapy of the lower respiratory system, the spraying of atomized solutions is contraindicated as producing physically heterogeneous aerosols, a large component of which would contribute to systemic toxicity without reaching the alveolar surfaces. If it is desired to confine therapy predominantly to the bronchioles and alveoli, the clinician should ascertain that the nebulizer of his choice produces with 5 per cent glycerin a fine smoke that floats in the air, rather than a spray capable of wetting objects placed a few inches from the orifice. A convenient test is to direct the nebulizer at a pane of glass adequately warmed to prevent undue condensation. Physical analysis of aerosols produced with nebulizers considered clinically efficient for treating pulmonary disease reveals a modal particle diameter of 1 or 2 microns. Particles of this size will reach the peripheral respiratory branches.

Inhalation of aerosolized penicillin is a form of topical application. Florey and Fleming at an early date emphasized the importance of the topical use of penicillin whenever possible, a point reiterated by Florey at the Twenty-First Clinical Congress of the Connecticut State Medical Society in September, 1946. In other reports the topical administration of high concentrations of penicillin combined with the anionic detergent, Aerosol OT (dioctyl ester of sodium sulfosuccinate), in the successful treatment of chronic osteomyelitis is described.[24–26] In the present study 34 subjects were treated with aerosols of the cationic detergent Zephiran (alkyl dimethyl benzyl ammonium chlorides in aqueous solution), employed as a solvent for antibiotics. In the treatment of any chronic disease, whether pulmonary infection or osteomyelitis, the existence of infective foci sheltered from the effects of routinely administered penicillin by fibrosis, purulent matter or avascularity is a serious problem. The local use of antibiotic solutions in combination with detergents whose pharmacology and toxicity have been studied[27,28] is based on the following primary considerations:

Antibiotics administered in detergent solutions may possess the obvious advantages associated with detergency: emulsifying properties and reduced surface tension. The breaking up of pus and cellular detritus in solutions of wetting agents has been shown by Palitz and Herman.[29] Detergents are employed in the treatment of empyema, ulcers and infected fractures and routinely for the disinfection of skin and mucous membranes. In the aerosol treatment of fibrosed and purulent areas of the respiratory tract by antibiotics it is evident that any substance that might increase the probability of effective bacteriostatic contact between micro-organism and the antibiotic is a desirable adjuvant.

The activity of both penicillin and streptomycin in vitro is synergistically enhanced by the presence of detergents. In fact, it has long been known that detergents may enhance the action of bactericidal and bacteriostatic agents generally.[30] Excluding detergents, we have observed a definite synergism of penicillin with 9-amino acridine hydrochloride and streptomycin, using *Staphylococcus aureus* among other test organisms. The wetting agents Aerosol OT and Zephiran Chloride also potentiate the activity of penicillin in vitro, although the effect is reduced in the presence of blood.[31] The activity of Zephiran with penicillin on *Staph. aureus* (strain 313, N.R.R.L.) is shown in Table 1. Viable organisms

were determined by dilution platings of samples taken from tryptose phosphate broth at one, six and twenty-four hours of growth at 37°C.

It is observed that in the presence of a combination of Zephiran and penicillin (at concentrations singly ineffective in checking the growth of *Staph. aureus*) the surviving bacteria have been reduced in number to less than 0.1 per cent (Table 1). In solid mediums the same concentration of Zephiran uncombined with penicillin reduces surviving bacteria to 2.5 x 10^4 per million (Zephiran, 1:700,000). A level of penicillin is chosen that reduces survivors to 10^5 per million (penicillin, 0.01 units per cubic centimeter). In penicillin-detergent combinations there are no survivors among 6.4 x 10^4 seeded bacteria.

TABLE 1. *Consecutive Assays of* Staph. aureus *from Tryptose Phosphate Broth Containing Penicillin and Zephiran, Singly and in Combination.*

Assay Time hr.	Tube No.	Contents	Bacteria Present per cc.
1	1	Zephiran (1:700,000)	6.8 x 10^6
	2	Penicillin (0.035 units per cubic centimeter)	9.3 x 10^6
	3	Zephiran (1:700,000); penicillin (0.035 units per cubic centimeter)	6.0 x 10^6
	4	Control	8.5 x 10^6
6	1	Zephiran (1:700,000)	8.3 x 10^6
	2	Penicillin (0.035 units per cubic centimeter)	1.6 x 10^6
	3	Zephiran (1:700,000); penicillin (0.035 units per cubic centimeter)	2.7 x 10^6
	4	Control	3.0 x 10^6
24	1	Zephiran (1:700,000)	1.0 x 10^9
	2	Penicillin (0.035 units per cubic centimeter)	8.4 x 10^7
	3	Zephiran (1:700,000); penicillin (0.035 units per cubic centimeter)	6.1 x 10^6
	4	Control	4.3 x 10^9

Although an undeniable gap exists between clinical results and animal experimentation it is perhaps significant that in investigations conducted for the Medical Division, Chemical Warfare Service, it was observed that the administration of penicillin and Zephiran aerosols to mice with experimental pulmonary disease results in a reduction of mortality compared with penicillin aerosol controls.

Antibiotic-detergent therapy, like multiple chemotherapy generally, may be instrumental in reducing the incidence of refractory drug-fast infection incurred during the course of treatment. Our colleague, Demerec,[32] has shown that among staphylococci (and presumably among most other ordinarily susceptible bacteria) penicillin resistance occurs spontaneously in the absence of penicillin by a process of mutation among a certain proportion of penicillin-susceptible organisms undergoing multiplication. The same considerations apply to streptomycin.[33] We believe that the insidious appearance of resistant bacterial strains during a therapeutic program may be assumed to depend on a process of artificial selection in vivo. This involves the elimination of susceptible bacteria and the survival of their more hardy mutant descendants to form an ensuing generation of resistant pathogens. Surviving as a result of inadequate therapy, these resistant organisms serve to complicate the problem of treatment and become a potential source of new infections that are resistant from the onset. Therefore, in all use of antibiotics in which selection to resistance may occur, it is most urgent to use a dose that will be effectively bacteriostatic for all organisms, including any that may have mutated to the initial step in the development of resistance. Antibiotics should be administered in large doses and with sufficient frequency to maintain bacteriostasis for the more resistant members of a heterogeneous bacterial population. When possible, local therapy should be instituted. The problem of drug fastness, of debated significance in clinical treatment with penicillin, appears destined to be of greater importance with increased use of streptomycin.[34, 35] On a genetic basis the likelihood that resistance will be developed by a micro-organism against two bacteriostatic agents used simultaneously is very small, being the product of two arithmetic fractions. These fractions represent the probability of resistance (mutation) occurring to protect the organism from either substance alone. If the interesting observations of Carpenter et al.[36] and our own studies on synergism can be interpreted in this manner, the use of multiple chemotherapy takes on particular significance and may prove to become an urgent necessity in the use of agents that depend on subtle metabolic mechanisms for their activity.

We are well aware that the use of antibiotic aerosols, particularly in combination with synergistic agents, is largely unexplored. The germicidal effects of wetting agents may be partially nullified by foreign materials[31, 37] or by variation in hydrogen ion concentration.[38] For this reason the principles expressed must be regarded primarily as working hypotheses. Our own clinical experience over a period of two years in the treatment of osteomyelitis and respiratory disease, however, leads us to believe that consideration of the accumulated case histories previously reported and presented below may lead to a wider clinical employment of multiple chemo-

TABLE 2. *Summary of Cases of Bronchiectasis, Bronchitis, Sinusitis and Miscellaneous Infections Treated with Penicillin Aerosol.**

Case No.	Age	Sex	Diagnosis	Duration of Treatment	Treatment	Duration of Illness	Organisms Recovered	Comment
	yr.			*da.*				
1	41	F	Bronchiectasis	18	50,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr.	Since childhood	Nonhemolytic *Staph. aureus*	No improvement after follow-up in 1 yr..; no 2nd-yr. follow-up available.
2	58	M	Chronic bronchiectasis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	14 yr.	Beta-hemolytic streptococcus and hemolytic *Staph. aureus*	Patient shows marked improvement, particularly in this year, when given larger dosage
3	70	M	Pneumonitis, with lung abscess, secondary to pneumonia	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	4 yr.	No cultures	Patient seen in October, 1946, and showed complete recovery; no roentgenographic evidence of parenchymal damage.
4	45	M	Chronic bronchitis, with hemoptysis		100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	1 yr.	*Escherichia coli*	Marked improvement; expectoration diminished from 180 to 4 cc. per day.
5	50	F	Chronic bronchitis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	5 yr.	*Staph. aureus* predominantly; *Esch. coli.*	Marked improvement; recent severe cold cleared up with routine bed rest; no excessive expectoration.
6	23	F	Post-virus pneumonia; questionable Boeck sarcoid with diffuse nodule infiltration.	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	6 wk.	*Esch. coli*, beta-hemolytic streptococcus, hemolytic *Staph. aureus* and *Monilia albicans*	Patient, graduate nurse who stated that she had contracted virus pneumonia from patient, was acutely ill and responded satisfactorily
7	43	F	Chronic bronchitis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	3 yr.	*Bacillus subtilis* and hemolytic *Staph. albus* in sinus drainage; *Staph. albus*, predominantly, in sputum	Complete recovery when seen in June, 1946; headaches associated with chronic sinusitis had entirely disappeared.
8	33	F	Chronic bronchitis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	10 yr.	Hemolytic *Staph. albus* and *B. subtilis*	Patient made good recovery and has no symptoms at present.
9	29	M	Acute exacerbation of chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	8 yr.	Nonhemolytic staphylococcus	Excellent result; prior to aerosolization patient had many operative procedures for sinus drainage; swelling in eyes entirely subsided.
10	36	F	Chronic bronchitis, with bronchiectasis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	4 yr.	Alpha-hemolytic streptococcus (viridans group)	Patient has made excellent improvement to date, but follow-up inadequate owing to brevity of time since treatment
11	45	F	Chronic bronchitis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	20 yr.	Nonhemolytic *Staph. albus* in sinus drainage	Improvement to date excellent, but 2 months' follow-up too limited for final opinion
12	65	F	Chronic bronchiectasis, with emphysema	10	50,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr.	15 yr.	Beta-hemolytic and alpha-hemolytic streptococcus, staphylococcus, *Esch. coli* and *Pseudomonas aeruginosa*	Patient unimproved
13	67	M	Bronchiectasis	10	50,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr.	10 yr.	Nonhemolytic *Staph. aureus*, nonhemolytic *Staph. albus* and *Klebsiella pneumoniae* (Type B)	Temporary improvement following treatment; patient now has recurrence and has been advised to have streptomycin treatment in view of gram-negative organisms.
14	30	F	Chronic diffuse bronchiectasis, with healed tuberculosis	6	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr.	11 yr.	Hemolytic *Staph. aureus*, hemolytic streptococcus, *M. albicans* and *K. pneumoniae* predominantly	Patient unimproved
15	67	M	Bronchiectasis	5	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr.	Since childhood	Beta-hemolytic streptococcus, hemolytic *Staph. aureus* and alpha-hemolytic streptococcus	Temporary improvement immediately after treatment. Follow-up later revealed patient unimproved.
16	38	M	Chronic diffuse pneumonitis	10	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr.	5 mo.	Beta-hemolytic streptococcus, nonhemolytic *Staph. aureus* predominantly	Patient seen in October, 1946, and was unimproved
17	44	M	Chronic sinusitis, with bronchial asthma	10	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr.	Since childhood	Alpha-hemolytic streptococcus and *M. albicans*; hemolytic *Staph. aureus*; beta-hemolytic streptococcus and *Esch. coli.*	Marked improvement. Patient recently had upper respiratory cold, but no recurrence of the asthma.
18	67	M	Bronchiectasis	10	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr.	10 yr.	*Staph. albus*; beta-hemolytic streptococcus predominantly; heavy growth of *Esch. coli*; negative for gram-positive cocci.	Patient made good improvement. His breathing was greatly helped by reducing infection and increasing vital capacity.
19	43	F	Bronchiectasis; questionable Boeck sarcoid.	10	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr.	2 yr.	Alpha-hemolytic streptococcus	Patient has improved, but has changed residence from New York to Arizona, which may be responsible for continued improvement
20	19	M	Bronchiectasis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 24 hr.	15 yr.	Nonhemolytic *Staph. albus* and *Staph. aureus*; nonhemolytic streptococcus predominantly.	Patient showed immediate improvement, but later had recurrence (one year). Recent attempts to follow up of no avail.

TABLE 2 (*Continued*).

Case No.	Age	Sex	Diagnosis	Duration of Treatment	Treatment	Duration of Illness	Organisms Recovered	Comment
	yr.			*da.*				
21	45	M	Chronic bronchiectasis, with asthmatic attacks	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 24 hr.	1 mo.	*Esch. coli*	Patient made immediate improvement. Recent follow-up cannot be obtained.
22	59	F	Chronic bronchiectasis, with sinusitis	7	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 24 hr.	1 yr.	Fungi resembling *M. albicans*; nonhemolytic streptococcus predominantly (gamma type).	Slight temporary improvement immediately after hospital discharge. No permanent improvement.
23	44	M	Chronic bronchiectasis, with sinusitis	14	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 24 hr.	14 yr.	Alpha-hemolytic streptococcus predominantly; few beta-hemolytic streptococci; few colonies of slightly hemolytic *Staph. aureus*; *B. subtilis*; *M. albicans*.	Patient made immediate improvement. Recent follow-up cannot be obtained.
24	51	M	Chronic sinusitis, with diffuse bilateral bronchiectasis	10	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr.	29 yr.	Predominantly *Staph. aureus*, hemolytic and nonhemolytic	Moderate improvement, but follow-up showed need for supplementary treatment now. This patient a physician.
25	45	F	Chronic pansinusitis	10	200,000 units of aerosolized penicillin dissolved in physiologic saline solution every 8 hr.	6 mo.	Alpha-hemolytic streptococcus predominantly; also many colonies of hemolytic *Staph. aureus* and several colonies of *Esch. coli*.	Follow-up one year after treatment indicates good improvement maintained
26	72	M	Chronic bronchiectasis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	Since childhood	Hemolytic streptococcus; *Staph. albus* predominantly.	Result unsatisfactory, probably owing to diffuse pneumonitis with clumps as result of submergent accident in childhood
27	57	M	Chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 12 hr.	14 yr.	*Staph. albus*, predominantly, and fungi in sinus drainage; *Esch. coli* predominantly in several colonies of alpha-hemolytic and few beta-hemolytic streptococci.	Immediate improvement, but follow-up showed some recurrence; over-all benefit derived, however.
28	51	F	Chronic bronchitis, with recurrent sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	10 yr.	Nonhemolytic streptococcus, some *Staph. aureus* and *Esch. coli*	Patient has not benefited by therapy; in fact, she considers herself more susceptible to colds since treatment.
29	22	M	Cold and productive cough	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	1½ yr.	*Esch. coli* predominantly; few nonhemolytic streptococci and staphylococci.	Result excellent until patient contracted cold, when sputum returned; sputum subsided when cold disappeared, however.
30	67	M	Chronic bronchiectasis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	3 yr.	*Staph. albus*; fungi resembling *M. albicans*; beta-hemolytic streptococci predominantly.	Temporary improvement; last report in December, 1946, indicated improvement not permanent.
31	43	M	Chronic bronchiectasis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	1½ yr.	*Staph. albus* predominantly; some *Staph. aureus* and beta-hemolytic streptococci.	Good result; patient states that there is great improvement, with little or no expectoration.
32	37	M	Chronic bronchitis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 12 hr.	15 yr.	Nonhemolytic streptococcus and *Staph. albus*	Good result; patient originally referred for surgery for chronic sinusitis; we did not endorse plan, and penicillin by nasal route helped recovery.
33	60	M	Chronic bronchitis with chronic sinusitis; uveitis and diabetes.	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	4 yr.	*Staph. albus* in sinus drainage; beta-hemolytic streptococci and some staphylococci in sputum.	Moderate improvement maintained since April, 1946
34	57	F	Chronic bronchitis	10	60,000 units of aerosolized penicillin dissolved in physiologic saline solution every 12 hr.	6 mo.	Few nonhemolytic streptococci; hemolytic *Staph. aureus* predominantly.	Patient made excellent improvement and states that she now has no expectoration
35	44	M	Bronchiectasis, with massive hemorrhage of lung	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	15 yr.	Hemolytic *Staph. aureus*, *Str. viridans* and *Staph. albus*; fungi resembling *M. albicans*.	Very satisfactory result; patient has had no hemorrhages and a minimum of expectoration.
36	66	M	Chronic bronchitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	25 yr.	Alpha-hemolytic streptococci predominantly; some fungi resembling *M. albicans*.	Moderate improvement, but result not entirely satisfactory
37	42	F	Bronchiectasis, with massive hemorrhage of lung	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	10 yr.	Nonhemolytic streptococci; staphylococci	Excellent improvement, which has been maintained since October, 1946
38	60	F	Bronchiectasis, with hemoptysis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	40 yr.	*Staph. albus*; nonhemolytic streptococci.	After many years of treatment elsewhere patient made remarkable recovery with, penicillin by nasal route
39	45	F	Acute exacerbation of chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr.	3 yr.	Nonhemolytic *Staph. albus*	Very satisfactory result obtained with penicillin by nasal route

*Supplementary parenteral treatment was given in each case as described above.

therapy and to a reconsideration of the topical treatment of infection, both with benefit to the patient. All material accumulated over a period of two and a half years is reported. Follow-up reports have been established in all these cases.

Method

Our original technic was to give the patient 50,000 units intramuscularly on admission to the hospital and to follow this with 10,000 every three hours for ten days. In many cases, to avoid unnecessary injections, we gave 50,000 units every twelve hours in Pendil for the required ten days. Intramuscular penicillin serves to supplement penicillin aerosol. Recently, to diminish the discomfort of frequent intramuscular injections, we have been giving 300,000 units of penicillin in 1 cc. of beeswax and peanut oil every twenty-four hours, since Romansky and Rittman[39] have demonstrated that an assayable blood level may thus be maintained for about one day. In subsequent discussions of the value of aerosol therapy, the possible therapeutic contributions of parenterally administered antibiotics are implied.

In preparation for aerosol therapy we now use 0.5 cc. of a 0.25 per cent solution of Neo-Synephrine in the nebulizer. This the patient deeply inhales before starting the treatment with penicillin. Neo-Synephrine is immediately followed by deep inhalation of 100,000 units of penicillin dissolved in 3 cc. of Zephiran in a 1:1000 aqueous solution every eight hours. The patient is carefully instructed concerning the basic anatomic and physiologic principles involved so that he will use forced expiration and then deeply inhale to the full limit of his vital capacity, simultaneously breathing in the aerosolized penicillin with the detergent. Emphasis on this important phase of the therapy is vital if the topical principle is to be fully exploited. The patient is instructed to prolong inhalation one or two hours by resting between each inhalation. When finished, to utilize more fully the penicillin that is retained on the walls of the glass nebulizer, 1 cc. of physiologic saline solution introduced into the same nebulizer is inhaled. This procedure is followed every eight hours for ten days. All patients have been hospitalized during the interval of treatment. In the hospital we were able to obtain the necessary bacterial cultures and to correct minor difficulties in technic. From the onset we were desirous of maintaining an adequate dosage of penicillin for a prolonged period so that the artificial selection of penicillin-resistant organisms, as described by Rammelkamp and Maxon,[40] could be avoided. In 4 cases, urticarial swelling and itching followed the administration of penicillin by inhalation.

Treatment of Chronic Sinusitis, Tracheobronchitis and Bronchiectasis

Chronic tracheobronchitis, often associated with bronchiectasis, pulmonary emphysema and sinusitis, has been the most frequent type of respiratory infection for which we have found penicillin aerosol to be of aid. The sulfonamides have been administered in aerosol form in the treatment of bronchiectasis by Stacey.[41] Olsen[10] has given penicillin aerosol to 7 patients hospitalized for pulmonary resection, stating that the method is the best available to prevent complications following complete or partial lobectomy for pulmonary suppurative disease. Among 8 cases of bilateral or inoperable bronchiectasis, Olsen reports immediate improvement in 7 with thinning and reduction of sputum, but with some later remissions. Segal and Ryder[13] suggest that periodic retreatment with aerosols may be necessary in the proper management of inoperable bronchiectasis. Barach[11] states that no improvement occurred in 3 of 7 cases of bronchiectasis associated with other bronchial or pulmonary infection, and of 4 improved patients remission was later evident in 2. Barach administered 100,000 to 200,000 units of penicillin as aerosol over a period of five to thirty-five days. Bobrowitz et al.[42] have also noted a tendency for remission to occur after treatment of bronchiectasis with intramuscular injections, intratracheal instillation and aerosolization of penicillin. The complete fibrotic reorganization and irreversible functional damage resulting from chronic bronchiectasis and bronchiolectasis make it probable that repeated bacterial infection follows the most thorough and effective therapeutic program. In the evaluation of improvement, allowance must be made for the usual seasonal fluctuations in cough, and no amelioration may be regarded as permanent without prolonged and possibly lifelong observation.

A chronic syndrome of sinusitis associated with either bronchitis or bronchiectasis is frequent (Table 2). Upper respiratory infection has been treated as a general problem with aerosolized and supplementary intramuscular penicillin. More recently, Zephiran in a 1:1000 solution has been used as a solvent for penicillin, to be given as an aerosol. The resulting turbid suspension forms a stable mist.

Among 21 patients with bronchiectasis treated by penicillin aerosol therapy, adequate subsequent observations extending up to two years have been obtained. Of these, 5 were not helped, 6 improved temporarily but relapsed, and 10 were definitely benefited. A possible contribution to improvement was temporary hemidiaphragmatic paralysis produced by crushing of the phrenic nerve in 2 of the improved patients, both of whom had experienced hemorrhage and hemoptysis. In the group with bronchitis, 1 patient was not relieved, 1 relapsed after temporary disappearance of symptoms, and 8 showed improvement. In addition, a patient with bronchitis was aided, but in this case the observation period since treatment extended only for two months. Aerosol treatment of sinusitis may be quite effective, and suitable instruments with affixed

nasal catheters may now be obtained.* Sixteen persons with sinusitis either singly or in combination with other respiratory ailments received penicillin in physiologic saline solution or Zephiran as an aerosol. Recent histories are available for 13 patients, of whom 10 showed clinical improvement with no relapse.

Diffuse Pulmonary Fibrosis with Limited Vital Capacity

Pneumoconiosis caused by prolonged exposure to silicon dust and characterized by nodular fibrosis and emphysema has been recognized as an occupational disease for many years.[43] Even when the proportion of inhaled silicon dioxide is relatively lower, as in certain coal-mining activities, a diffuse perilymphatic fibrosis is often associated with anthracosis. The resultant dyspnea may be a severe physical handicap.

It is now realized that the proper control of occupational pneumoconiosis should be prophylactic. Yet persons engaged in mining activities before adequate protection had been made to prevent irreversible fibrotic damage to the lung present a serious and tragic problem. Any therapeutic agent that will help this group with reduced vital capacity demands consideration by physicians engaged in industrial medicine. Treatment with penicillin aerosol has been found to be of definite benefit in decreasing the respiratory deficiency noted in diffuse pulmonary fibrosis of occupational origin. The following brief abstracts of case reports are of interest.

Case 40. A 68-year-old man with extensive fibrosis of both lungs had worked for many years in a granite quarry; any activity produced marked dyspnea. Examination disclosed many rales in the chest. Aerosolized penicillin was given in October, 1944, producing great relief from the dyspnea. A cerebral accident, with hemiplegia, recently occurred, and the patient is now in a county hospital. Dyspnea presents no problem at present.

Case 41. A 56-year-old man who had been a coal miner most of his life had considerable dyspnea in April, 1945, with limited activities as a doorman. Aerosolized penicillin was given in April, 1945, and the patient has carried on all his duties with no discomfort. At present he has been urged to return for a yearly repetition of treatment but refuses because he has no symptoms and feels in good health.

Since the vital capacity lost as a result of pulmonary fibrosis cannot be replaced, the cause of clinical improvement subsequent to the use of penicillin aerosol in pneumoconiosis is obscure. The marked and unexpected regression in symptoms of dyspnea may have been due to a reduction in associated infection, with a resultant increase in vital capacity. By all clinical signs, both patients have been greatly helped. Physicians in mining areas confronted with the problem of silicosis and anthracosis are urged to investigate and report on a larger series of such cases in which penicillin aerosol has been used. The cases discussed above are insufficient to permit any categorical conclusions.

*DeVilbiss 640, obtainable from DeVilbiss Company, 111 Eighth Avenue, New York City.

Severe Asthma

The treatment of infective intrinsic asthma by penicillin aerosols has been reported by Barach[11] and by Segal and Ryder.[13] Barach summarizes the result of his favorable experience, stating that of 4 patients relieved of asthmatic symptoms for one or two months but with subsequent remission, 2 were successfully treated by a second course of aerosol therapy. Since most asthma is extrinsic in origin it is essential that a careful diagnosis be made to determine the etiologic role of bacteria before a program of penicillin aerosols is begun.

Segal and Ryder[13] described no marked change in bronchospasm following penicillin aerosol therapy administered to 6 asthmatic patients. The excellent result obtained in the following case may have depended in part on the use of a germicidal detergent (Zephiran in a 1:1000 aqueous solution) as a solvent for the penicillin:

Case 42. A 16-year-old boy with a history of severe infective intrinsic asthma for 8 years, which had been getting progressively worse, could not play or move about with companions. At present, 18 months after the administration of aerosolized penicillin, he has had only one attack and is able to carry on all normal activities for his age with no discomfort. In November, 1946, he was seized with an upper respiratory infection, and 48 hours later he had an asthmatic attack. He was immediately hospitalized, and aerosol therapy instituted with penicillin and streptomycin, each for five days. The patient responded satisfactorily and now has no symptoms.

Prevailing opinions on the value of asthma penicillin aerosols in the treatment of asthma are contradictory and will presumably remain so, in view of the complex physiologic nature of the disease. Asthma should properly be considered a symptomatic response to a wide variety of conditions, including allergic, toxic and psychogenic factors; therefore, it does not appear probable that treatment of associated infection will always be successful. Yet, in our opinion, and that of Barach,[11] aerosol therapy may be a satisfactory method of treatment if justified by bacteriologic studies.

Putrid Lung Abscess

In 1942 Maier and Grace[44] reported the distinct clinical entity of putrid empyema, recommending treatment through surgical drainage by open thoracotomy. Confirmation was afforded the previous observation of Neuhof and Hirshfeld[45] on the anaerobic nature of the causative micro-organisms. Infection with anaerobic streptococci and staphylococci, mixed with spirochetes and aerophilic bacteria, has been described not only in putrid empyema but also in putrid lung abscess. Since putrid empyema develops most frequently from the intrapleural rup-

ture of bronchiectatic or abscessed regions of the lung, particular interest is attached to the adequate control of these contributory diseases. The aim of medicine should be preventive rather than remedial.

In the following case, aerosolized penicillin in Zephiran, supplemented by parenteral penicillin, was successful in curing a putrid lung abscess without surgical interference:

CASE 43. This patient gave a history of so-called "pneumonia" for 3 weeks, which had been getting progressively worse, with expectoration of ½ to 1 cupful of foul, putrid sputum a day and a daily temperature of 103°F. X-ray study showed a large lung abscess in the right upper lobe. Penicillin was given parenterally, with penicillin in Zephiran aerosol (for 10 days), and the patient promptly made an uneventful recovery. At follow-up study 3 months later, there were no symptoms. X-ray examination showed complete resolution of the abscess.

The topical administration of penicillin-detergent solutions may ultimately prove to be of aid in the elimination of gram-negative bacilli and penicillinase-producing bacteria symbiotically involved in putrid lung abscess and ordinarily unchecked by penicillin alone. It is essential that a detergent capable of acting in high dilution, whose antibacterial properties have been studied, be utilized. At the same time, a conservative distinction must be drawn between the accepted germicidal potentialities of detergents in vitro and their largely undetermined value as inhalational aerosols. Without undue optimism it is believed that the prompt and judicious use of aerosol therapy will, on occasion, prevent the desperate clinical picture of advanced anaerobic infection. When surgery is indicated for pulmonary disease, preoperative treatment with aerosols should be of value, according to the principles elaborated by Olsen.[10]

ACTIVE PULMONARY TUBERCULOSIS

Since the tubercle bacillus is not sensitive to penicillin concentrations ordinarily attainable, it is at once evident that penicillin aerosol does not afford the promise of streptomycin in the treatment of tuberculosis. It is well known, however, that a considerable degree of damage in tuberculosis of the lungs is caused by associated bacteria, notably staphylococci and streptococci. If these secondary invaders could be controlled by penicillin, it was thought that a possible resultant reduction in bacterial flora and general toxemia might provide an opportunity for the natural defenses of the body to effect an arrest or regression of the disease.

The following are brief abstracts of cases treated for secondary infection with penicillin aerosol:

CASE 44. This 26-year-old patient had pulmonary tuberculosis of the left upper lobe, with multiple cavities, positive sputum and a high sedimentation rate (77 mm. in 1 hour by the Westergren method). The phrenic nerve was crushed, and hemidiaphragmatic paralysis was done, with aerosol therapy as described above. The patient was not helped.

CASE 45. This 34-year-old patient gave a history of tuberculosis of the right upper lobe of 10 years' duration. The sputum was positive. Frequent rest and artificial pneumothorax had been unsatisfactory; aerosolized penicillin was not helpful, but was regarded as an important preoperative aid to a two-stage thoracoplasty. The sputum was negative for a period, and the patient actively engaged in business. The treatment was perhaps instrumental in changing a case of acute pulmonary tuberculosis to a chronic one by control of the secondary infection in the lung and diminishing of systemic toxemia. A preliminary phrenic-nerve operation had been done. The possibility that temporary improvement would have occurred spontaneously without treatment cannot be ruled out. Four months after discontinuation of treatment a positive sputum and evidence of activity in the lung were found.

CASE 46. This 44-year-old patient had bilateral pulmonary tuberculosis, with cavitation in the left lung. The sputum was positive, and the sedimentation rate was high. Aerosolized penicillin was not helpful.

CASE 47. A 40-year-old woman had extensive bilateral pulmonary tuberculosis. There was a high sedimentation rate (78 mm. in 1 hour). The sputum was positive. Aerosolized penicillin was used, but the vital capacity was so limited that the patient could not follow the prescribed technic of deep inhalation. This patient died four months later from pulmonary tuberculosis. The use of aerosolized penicillin was unsatisfactory.

These 4 patients with advanced tuberculosis were treated before streptomycin became available and were not benefited by efforts to control secondary bacterial invaders with aerosolized penicillin.

Streptomycin as an aerosol has been employed by Nichols and Herrell[46] and by Olsen[47] in the treatment of bronchiectasis with gram-negative involvement, and also by Hinshaw, Feldman and Pfuetze[48] in the therapy of tuberculosis. It is perhaps significant that streptomycin has been reported to be less diffusible in the body than penicillin — an observation indicating possible advantages in the topical treatment attainable by aerosolization. The use of streptomycin as an aerosol in the treatment of pulmonary tuberculosis appears, a priori, to be worthy of extensive investigation. We have had the opportunity to hear both Hinshaw and McDermott report their experiences in the therapy of tuberculosis with parenteral streptomycin. Since streptomycin as now administered appears in some cases to be merely a palliative,[48] a co-ordinated therapeutic program may be required, involving suppression of the tubercle bacillus and any secondary infection, together with adequate diet and rest for the patient. Efforts to increase liver efficiency may do a great deal to diminish damage by bacterial toxins. By aerosol therapy it may be possible to deliver streptomycin topically and in larger doses than can be placed in the lung by parenteral methods. One of us (E. J. G.) believes that thoracoplasty should not be done until the more conservative plan of therapy has been adequately tried. With a larger output of streptomycin gradually becoming available, a method of topically placing this antibiotic or other chemotherapeutic agents in more direct contact with tuberculous lesions in the lung might have a profound effect in limiting the magnitude of thoracic surgery required in the treatment of pulmonary tuberculosis and in altering the course of the disease.

In addition to the administration of aerosolized penicillin in Cases 44–47, a small series of patients were treated with streptomycin aerosol, the detergent Zephiran in a 1:1000 aqueous solution being used as a solvent. In the topical eradication of acid-fast bacteria isolated in fibrosed, calcified or caseous tubercles the potential significance of an actively germicidal and detergent aerosol becomes obvious. Yet we do not at present know if the necessary level of germicidal and detergent efficiency can be reached without associated toxic and hemolytic effects. Our present clinical experience is too inadequate to justify report of more than the arrest of pulmonary tuberculosis with symptomatic improvements in 4 patients treated with streptomycin in Zephiran, 1 of whom (Case 49) received direct intrapleural instillation for bronchopleural fistula.

Case 48. This 36-year-old patient stated that in 1934 a diagnosis of left pulmonary tuberculosis had been made. Artificial pneumothorax was given until 1938, when pleural fluid was aspirated and *Mycobacterium tuberculosis* was found. Subsequently, the patient developed a chronic tuberculous empyema that had drained constantly for 8 years, and entered the Grace Clinic in 1941. All accepted methods of treatment, including complete thoracoplasty of the left side, were used, but empyema continued to drain. Biopsy of the visceral and parietal pleura showed a classic picture of tuberculosis. On October 14 and 15, 1946, a solution was made of 20 cc. of Zephiran chloride aqueous solution (1:1000) with 1 gm. of streptomycin and 5 cc. was injected directly into the pleural cavity every 5 hours for six doses. Five days later the chronic tuberculous sinus tract closed for the first time in 8 years, and now, 1 year later, it is still closed. The clinical condition is now good.

Case 49. A diagnosis of pulmonary tuberculosis in this 37-year-old woman was made in 1929. A continuous artificial pneumothorax was given. The patient, when 2 months pregnant, developed a bronchopleural fistula with a fluid level 9 cm. above the left leaf of the diaphragm. Empyema fluid drained into the fistula. There was a continuous cough. The patient spoke with difficulty. She appeared moribund when seen on November 14, 1946. The immediate problem was supportive treatment with control of the empyema and bronchopleural fistula of the left side. For the following 7 days 1 gm. of streptomycin dissolved in 10 cc. of 1:1000 aqueous solution of Zephiran was injected into the pleural space, and 200,000 units of streptomycin and 100,000 units of penicillin were administered intramuscularly every 12 hours in beeswax and peanut oil for 6 weeks. The patient gave birth prematurely on November 22, 1946. The baby died. The hacking cough and copious expectoration started to subside after the intrapleural instillation of streptomycin detergent and have now been eliminated. The fluid level was reduced to 3.7 cm. All clinical and laboratory data confirm the obvious symptomatic improvement. The seriousness of the illness may be gauged by the fact that the patient cannot recall anything that took place during the first ten days of her confinement to the hospital. Aerosolized penicillin therapy was attempted and stopped because of great distress to the patient, with some hemoptysis. The possibility of mediastinal shifting and flutter with consequent circulatory and respiratory embarrassment may preclude forced breathing of aerosols when bronchopleural fistula is present.

Case 50. A 29-year-old patient was known to have had bilateral tuberculosis for 3 years. She entered the Grace Clinic on November 13, 1946, with a hydropneumothorax of the right side. Diffuse mottling and infiltration were noted throughout the left portion of the chest. On the right a temporary hemidiaphragmatic paralysis was accomplished by crushing of the right phrenic nerve. On December 20 the patient was given 100,000 units of penicillin and 200,000 units of streptomycin as aerosol in 3 cc. of a 1:1000 solution of Zephiran every 8 hours, together with 200,000 units of streptomycin in beeswax and peanut oil every 12 hours. Penicillin-streptomycin-detergent aerosol was continued for 3 weeks. Streptomycin given intramuscularly has been continued to date.

Case 51. A 28-year-old woman had been seen at various intervals since March 7, 1945. She had no specific complaint except slight colds, with a minimal cough at various times, and fatigue. X-ray studies of the chest on six occasions from the first visit failed to establish any definite diagnosis. On October 30, 1946, the patient had an acute cold and cough. Routine x-ray study of the chest on that date was reported as showing a moderate infiltrative lesion involving the left apex. In the first interspace anteriorly there was a small cavity in this apical lesion. The patient was hospitalized immediately, and antibiotic therapy started. Penicillin and streptomycin were given, with detergent Zephiran Chloride in a 1:1000 solution as an aerosol and also systemically in peanut oil. X-ray studies on January 2, 1947, revealed moderate fibrosis in the left apex. The cavity was no longer visible. There was no definite evidence of active infiltration at that time. The patient could take aerosolized streptomycin and penicillin for only 1 month, but from the onset of therapy she had had 0.5 gm. of streptomycin daily. Treatment was begun on November 1, 1946, and is being continued to date. This patient has clinically made a satisfactory recovery, as confirmed by x-ray examination, but in spite of the clinical improvement a high sedimentation rate (38 mm. in 1 hour by the Westergren method) indicates the importance of not permitting clinical or x-ray data alone to determine the plan of a patient's activity.

Any attempt at present to judge the merit of the therapeutic programs outlined would be premature. Yet there can be no doubt that symptomatic improvement has occurred, and it is highly probable that death was imminent in Case 49 before treatment was instituted. Complete laboratory reports have been kept, and include findings of negative sputum after treatment. As a negative finding, however, the absence of *Myco. tuberculosis* in the sputum is regarded as of doubtful diagnostic value. No vestibular disturbances have been reported by the patients. Although not properly within the scope of a paper on aerosols, Cases 48 and 49 have been included as examples of the local employment of antibiotic-detergent therapy, which assumes significance in the light of Hinshaw's findings. Hinshaw et al.[48] state that among 7 cases of tuberculous empyema treated with streptomycin routinely, definite improvement was noted in only 1. The refractory nature of tuberculous empyema is ascribed in part by these investigators to the granulomatous nature of the diseased pleura. The reduced surface tension of streptomycin detergent may afford a more efficient infiltration of superficial granulomatous processes.

One of us (E. J. G.) has had the opportunity to participate in surgical treatment of pulmonary tuberculosis during the last two decades, in county hospitals, private sanatoriums and private practice. During that period the radical surgical procedures advocated above have been employed. In the late follow-up study of patients treated by radical surgery it is tragically evident that surgical procedures are often far from ideal. It is now generally agreed that the accepted conservative procedure of bed rest, adequate diet and nursing care remains the method of choice in the treatment of tuberculosis. Anti-

biotic-detergent aerosol therapy should be regarded as a supplement to the conservative management of tuberculosis, an approach that should be thoroughly explored before resorting to surgery. Since others have reported the arrest of pulmonary tuberculosis with parenteral streptomycin,[48] any proper evaluation of topical streptomycin-detergent therapy must await the accumulated experience of careful observation over a long period.

Summary

The mechanical equipment necessary for effective aerosol therapy is preferably simple, consisting of a suitable nebulizer for oral inhalation and a nebulizer with attached cannulae for nasal inhalation. The distinction between atomizers and nebulizers should be understood by the physician. The medical use of aerosols demands a basic knowledge of the fundamental physical principles involved in the behavior of inspired particles of different sizes.

Aerosol therapy is considered a form of topical treatment. Topical administration of antibiotics in detergent solutions may provide the physical advantages associated with reduced surface tension and the antibacterial advantages contingent on synergism and the reduced likelihood of drug-fast infection.

Clinical experience of more than two years has shown antibiotic aerosol therapy to be a valuable supplement to parenteral treatment of respiratory disease, including intrinsic infectious asthma, bronchitis, bronchiectasis, sinusitis and, more recently, tuberculosis. Except in selected cases, aerosol therapy should be attempted before surgery is resorted to.

References

1. Heubner, W. Über Inhalation zerstaübter Flüssigkeiten. *Ztschr. f. d. ges. exper. Med.* **10**:269-332, 1919.
2. Lageder, K. Untersuchungen über den Einfluss inhalierten Adrenalins auf die Lungenventilation beim Asthma bronchiale und über dessen Allgemeinwirkung. *Beitr. z. Klin. d. Tuberk.* **83**:605-618, 1933.
3. Castex, M. R., Capdehourat, E. L., and Pedace, E. A. Inhalación de substancias nebulizadas: comprobación experimental de su poder de penetración a nivel del aparato respiratorio. *Arch. argent. de enferm. d. ap. respir. y tuberc.* **9**:1-11, 1941.
4. Bruere, P., and Gauchard, F. Neutralisation des produits agressifs par ultradispersion des liquides. *Bull. d. docteurs en pharmacie des Universités de France* **1**:(Jan.-Feb.), 1937.
5. Abramson, H. A. Improved inhalation therapy of asthma. *Arch. Phys. Therapy* **21**:612-615, 1940.
6. Dautrebande, L. Aérosols médicamenteux: pénétration par voie intraartérielle transpulmonaire d'agents pharmaco-dynamiques. *Schweiz. med. Wchnschr.* **71**:445, 1941.
7. Abramson, H. A. Principles and practice of aerosol therapy of lungs and bronchi. *Ann. Allergy* **4**:440-456, 1946.
8. Hufferd, R. W. Penicillin aerosol: contribution of Chemical Warfare Service to medicine. *Science* **104**:498, 1946.
9. Bryson, V., Sansome, E., and Laskin, S. Aerosolization of penicillin solutions. *Science* **100**:33-35, 1944.
10. Olsen, A. M. Nebulized penicillin: preliminary report of its role in management of surgical bronchiectasis. *Proc. Staff Meet., Mayo Clin.* **20**:184-194, 1945.
11. Barach, A. L., Silberstein, F. H., Oppenheimer, E. T., Hunter, T., and Soroka, M. Inhalation of penicillin aerosol in patients with bronchial asthma, chronic bronchitis, bronchiectasis and lung abscess: preliminary report. *Ann. Int. Med.* **22**:485-509, 1945.
12. Vermilye, H. N. Aerosol penicillin in general practice. *J. A. M. A.* **129**:250-257, 1945.
13. Segal, M. S., and Ryder, C. M. Penicillin aerosolization in treatment of serious respiratory infections: preliminary report. *New Eng. J. Med.* **233**:747-756, 1945.
14. Humphrey, J. H., and Joules, H. Penicillin inhalation in pulmonary disease. *Lancet* **2**:221-225, 1946.
15. Southwell, N. Inhaled penicillin in bronchial infections. *Lancet* **2**: 225-227, 1946.
16. Eckman, M., Rumsey, C. C., Jr., Barach, B., and Barach, A. L. Demand apparatus for automatic delivery of aerosols during inspiration. *J. Lab. & Clin. Med.* **30**:608-610, 1945.
17. Barach, A. L., Garthwaite, B., Soroka, M., and Anderson, F. F. Apparatus for introduction of penicillin aerosols into nasal accessory sinuses with case report of patient with chronic sinusitis. *Ann. Int. Med.* **24**:97-103, 1946.
18. Abramson, H. A. Aerosol therapy of lungs and bronchi with special reference to penicillin and hydrogen peroxide. *Bull. New Eng. M. Center* **8**:97-106, 1946.
19. Hatch, T. F. Behavior of microscopic particles in air and in respiratory system. In *Aerobiology*. Edited by F. R. Moulton. 289 pp. Publication No. 17, American Association for the Advancement of Science. Washington, D. C., 1942. Pp. 102-105.
20. Farinas, P. L. Mucosography of respiratory tract. *Tr. Radiological Soc. North America, 27th Annual Meeting* **39**:84-87, 1942.
21. Morse, F. W. Penicillin spray by bulb atomizer in respiratory infections. *J. A. M. A.* **132**:272-278, 1946.
22. Barach, A. L., Molomut, N., and Soroka, M. Inhalation of nebulized promin in experimental tuberculosis: sodium P, P'-diaminodiphenylsulfone-N, N'-didextrose sulfonate. *Am. Rev. Tuberc.* **46**:268-276, 1942.
23. Edlin, J. S., Bobrowitz, I. D., Safford, F. K., Jr., and Butler, F. S. Promin inhalation therapy in pulmonary tuberculosis. *Am. Rev. Tuberc.* **50**:543-555, 1944.
24. Grace, E. J., and Bryson, V. Topical use of concentrated penicillin in surface-active solution. *Arch. Surg.* **50**:219-222, 1945.
25. *Idem.* Nonoperative treatment of osteomyelitis with penicillin. *J. A. M. A.* **130**:841-844, 1946.
26. *Idem.* Chronic osteomyelitis in war wounded: report of two veterans discharged with intractable osteomyelitis and successfully treated with local penicillin detergent therapy. *New York State J. Med.* (in press).
27. Reiner, L. Activity of anionic surface active compounds in producing vascular obliteration. *Proc. Soc. Exper. Biol. & Med.* **62**:49-54, 1946.
28. *Zephiran Chloride.* Reprint by Winthrop Chemical Company, 1944.
29. Palitz, L., and Herman, M. Treatment of tuberculous and mixed infection empyema with new irrigating solutions. *Quart. Bull., Sea View Hosp.* **6**:181-196, 1941.
30. Petroff, S. A., and Schain, P. Enhancement of bactericidal properties of well known antiseptics by means of detergents. *Quart. Bull., Sea View Hosp.* **5**:372-384, 1940.
31. Bryson, V. Unpublished data.
32. Demerec, M. Production of staphylococcus strains resistant to various concentrations of penicillin. *Proc. Nat. Acad. Sc.* **31**: 16-24, 1945.
33. *Idem.* Personal communication.
34. Youmans, G., Williston, E. H., Feldman, W. H., and Hinshaw, H. C. Increase in resistance of tubercle bacilli to streptomycin: preliminary report. *Proc. Staff Meet., Mayo Clin.* **21**:126, 1946.
35. Finland, M., Murray, R., Harris, H., Kilham, L., and Meads, M. Development of streptomycin resistance during treatment. *J. A. M. A.* **132**:16-21, 1946.
36. Carpenter, C. M., Bahn, J. M., Ackerman, H., and Stolsinger, H. E. Adaptability of gonococcus to four bacteriostatic agents, sodium sulfathiazole, rivanol lactate, promin, and penicillin. *Proc. Soc. Exper. Biol. & Med.* **60**:168-171, 1945.
37. Baker, Z., Harrison, R. W., and Miller, B. F. Inhibition by phospholipids of action of synthetic detergents on bacteria. *J. Exper. Med.* **74**:621-637, 1941.
38. Gershenfeld, L., and Milanick, V. E. Bactericidal and bacteriostatic properties of surface tension depressants. *Am. J. Pharm.* **113**: 1-21, 1941.
39. Romansky, M. J., and Rittman, G. E. Penicillin blood levels for twenty-four hours following single intramuscular injection of calcium penicillin in beeswax and peanut oil. *New Eng. J. Med.* **233**:577-582, 1945.
40. Rammelkamp, C. H., and Maxon, T. Resistance of *Staphylococcus aureus* to action of penicillin. *Proc. Soc. Exper. Biol. & Med.* **51**: 386-389, 1942.
41. Stacey, J. W. Inhalation of nebulized solutions of sulfonamides in treatment of bronchiectasis. *Dis. of Chest* **9**:303-306, 1943.
42. Bobrowitz, J. D., Edlin, J. S., Bassin, S., and Woolley, J. S. Penicillin in treatment of bronchiectasis: preliminary report. *New Eng. J. Med.* **234**:141-147, 1946.
43. Betts, W. W. Chalicosis pulmonum or chronic interstitial pneumonia induced by stone dust. *J. A. M. A.* **34**:70-74, 1900.
44. Maier, H. C., and Grace, E. J. Putrid empyema. *Surg., Gynec. & Obst.* **74**:69-74, 1942.
45. Neuhof, H., and Hirshfeld, S. Suppurative pleuritis in children: its pathogenesis, diagnosis and treatment. *Am. J. Dis. Child.* **44**: 973-993, 1932.
46. Nichols, D. R., and Herrell, W. E. Streptomycin: its clinical uses and limitations. *J. A. M. A.* **132**:200-206, 1946.
47. Olsen, A. M. Streptomycin aerosol in treatment of chronic bronchiectasis: preliminary report. *Proc. Staff Meet., Mayo Clin.* **21**:53, 1946.
48. Hinshaw, H. C., Feldman, W. H., and Pfuetze, K. H. Treatment of tuberculosis with streptomycin: summary of observations on one hundred cases. *J. A. M. A.* **132**:778-782, 1946.

SERVICES OFFERED TO THE PHYSICIAN BY THE MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH*

VLADO A. GETTING, M.D.†

BOSTON

IN 1850 Lemuel Shattuck, a representative in the General Court of Massachusetts and a bookseller in Concord, alarmed to find that so many persons died in the prime of life, presented the first sanitary survey, entitled "Report of a General Plan for the Promotion of Public and Personal Health," to the General Court. In 1869 the first state board of health in the country was established by the General Court in Massachusetts. This Board was authorized to take cognizance of the interest of health and life among the citizens of Massachusetts, and to make sanitary investigations and inquiries concerning the people, the causes of disease, especially of epidemics, the sources of mortality and the effects of localities, employments, conditions and circumstances on the public health, as well as to gather information regarding such matters as it may deem proper for diffusion among the people. In subsequent legislation, the Massachusetts Department of Public Health was given broad authority, which has continued to increase, and is now charged with the following responsibilities: to make investigations of the sale of drugs and food and adulterations thereof; to advise the government and others of sanitary conditions in public institutions; to have oversight of inland waters and sources of water supply, as well as vaccine institutions, and to produce and distribute antitoxin and vaccine lymph and such specific serums for protective inoculations, diagnosis or treatment against typhoid fever and other diseases as the Department may from time to time deem advisable; to make annual examinations of all main outlets of sewers and drainage of the towns of the Commonwealth; to define diseases dangerous to the public health; to investigate contagious diseases; to furnish remedies for ophthalmia neonatorum; and to make minimum isolation and quarantine regulations. Many other responsibilities too long to list in this presentation have been assigned to the Department of Health.

Passing through many vicissitudes of organization, the Board of Health eventually assumed its present form in 1914 as a department of public health with an advisory public-health council and a commissioner as the administrative executive officer. It now employs approximately eighteen hundred people and expends an annual budget of about $8,000,000 derived from state, federal and private funds. The Department of Public Health has become responsible not only for the preventive aspects of public health but also for the promotion of optimal health and for the administration of medical-care programs; it is also charged with the direction of five state institutions.

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†Commissioner, Massachusetts Department of Public Health.

ORGANIZATION

The Commissioner, appointed for a period of five years by the Governor, is charged with the administration of the laws relative to health and sanitation and the regulations of the Department. He is required by law to prepare rules and regulations for the consideration of the Public Health Council and to direct employees of the Department to assist in the study, suppression or prevention of diseases in any part of the Commonwealth. Annually, he must submit to the Council a report containing recommendations regarding health legislation. He is required to be a physician schooled in sanitary science and experienced in public-health administration. He is the executive and administrative head of the Department and acts *ex officio* as chairman of the Public Health Council.

The Public Health Council, consisting of the Commissioner and six other members, meets at least once a month. Members are appointed by the Governor, one each year for a term of six years. The Council is required to promulgate rules and regulations, take evidence in appeals, hold hearings and discharge its duties as required by law. Hearings may be held by the Commissioner or by a director of a division of the Department if so authorized by the Commissioner and Council.

Divisional Organization

Because of the complex field activities, the Department is divided into the following sections: Administration, Biologic Laboratories, Cancer and Other Chronic Diseases, Communicable Diseases, Dental Health, Food and Drugs, Local Health Administration, Maternal and Child Health, Sanitary Engineering, Tuberculosis and Venereal Diseases.

Administration. This division, whose director is the Commissioner, is concerned primarily with the over-all administration of the Department, including physical and personnel matters, the development of rules and regulations, state and federal legislation, the dissemination of information through the Bureau of Health Information, the licensing of hospitals and the conduct of the Hospital and Health Center Survey and Plan, as authorized by Public Law 725, whereby Massachusetts is to receive a sum

of $8,000,000 over a period of five years, provided it be matched by double this amount in local or state funds, for assistance in the construction of health centers and hospitals, which are included in a plan now being developed under the direction of a special commission appointed by the Governor. A survey of hospitals and public-health centers is being completed to determine the actual needs of the Commonwealth, and the formulated plan is to provide coverage to meet existing needs.

Through the efforts of the Bureau of Hospital Licensing, improvements have been made in hospital staff organization, hospital records, obstetric care and the management of nurseries for the newborn. The Division of Administration advises local boards of health, voluntary health associations and professional organizations and consults them regarding the administration of the Department. It acts as a co-ordinating or liaison group with other governmental departments. The Commissioner serves as a member of the Milk Regulation Board and the Rating Board, and, most important, he also serves as a member of the Massachusetts Approving Authority for Medical Schools. This last organization has been effective in raising the standards for medical practice in Massachusetts. The Department of Public Health receives advice and federal grants-in-aid from the United States Public Health Service and the Children's Bureau, both in the Federal Security Agency. These funds are received for the following purposes: from the Public Health Service for venereal-disease control, tuberculosis control, general public health, industrial hygiene, cancer, hospital construction and survey; and from the Children's Bureau for maternal and child health, crippled-children's services and emergency maternal and infant care. Private funds are also expended for various specifically designated purposes.

Dental Health. This is the newest division of the Department and is primarily concerned with the promotion of dental-health education, the development of programs for the prevention of dental caries, the promotion of dental clinics for children and the dissemination of information relative to the care of teeth of children and adults. At present the Department is not conducting any service program except through well-child conference demonstrations in which dentists and dental hygienists make examinations and inspections of teeth for the information of parents, referring the children to the family dentists for treatment.

Food and Drugs. This division is truly the policeman of the Department and is primarily concerned with the sanitation and safety of foods and, secondly, with the purity of contents and the consumer value of foods and drugs. Inspections are made of all types of food-manufacturing establishments, including bakeries, slaughtering houses, poultry-slaughtering houses, pasteurization and other milk-handling concerns, wholesale and retail stores, cold-storage plants, soft-drink manufacturers and other food-processing establishments and restaurants. In addition, samples of many foods and drugs, as well as filling material of mattresses and upholstered furniture, are collected for analysis for adulteration, misbranding or safety. This assures the consumer that he is buying what he thinks he is buying, and that the food that he consumes is not only nutritious but also safe and sanitary. Through the Division of Food and Drugs licenses are issued to manufacturers and wholesale distributors of narcotic drugs. Routine check-up examinations are made on pharmaceutical products, especially those liable to deterioration (such as vitamin B_1 and digitalis), and on the accuracy of druggists in filling prescriptions. Notification to physicians is made of products determined harmful or dangerous to use.

Maternal and Child Health. This division is responsible for the promotion of prenatal care, for the development of a program for the care of premature infants, for the institution of refresher courses for physicians, for the conduct of well-child conferences and for the promotion of both preschool and school health programs. It has developed the Massachusetts vision test, which has replaced the Snellen chart, and is now promoting audiometer testing of the hearing of the children. Audiometer testing is done in groups and checked on an individual basis. Children who have apparent visual or hearing defects are referred to physicians for follow-up study. This division is also responsible for the administration of the Crippled Children Services — a program that has been co-ordinated with the activities of the District Medical Societies. Consultants for the state clinics are available together with a corps of other specialists, such as physical therapists, nurses, medical social workers and nutritionists, to assist in the care of children who are referred by physicians or social agencies. Any child may obtain diagnostic services, but only children whose families cannot afford to pay for medical and hospital care are accepted for treatment. One of the war activities has been the Emergency Maternity and Infant Care Program, which is in the process of gradual liquidation. Under this program any woman who was eligible prior to June 30, 1947, may receive benefits for maternity care. This includes the payment of physicians in accordance with the fee schedules set up by the Children's Bureau, and hospital services in accordance with schedules for payment to hospitals on a cost basis. The number of maternal cases cared for under this program as of May 1, 1947, was 32,643, including 15,668 from September, 1943, to December 31, 1944; 10,072 in 1945; 6284 in 1946; and 619 from January 1 to May 1, 1947. Servicemen's children under one year of age are eligible for health supervision and pediatric care on a similar schedule of fees to physicians and a payment based on cost to hospitals. The total number of children as of May 1, 1947, was 9255, including 2521

from September, 1943, to December 31, 1944; 3117 in 1945; 2833 in 1946; and 784 from January 1 to May 1, 1947. The Division is particularly concerned with the development of a school health program in co-operation with the Department of Education and, it is hoped, the inauguration of a local school-physician consultant service for this purpose.

Sanitary Engineering. One of the largest divisions of the Department is that of Sanitary Engineering, which is responsible for the supervision of water supplies, sewage disposal and drainage systems and for advice to cities, towns and persons on water supply and sewerage problems. All construction or reconstruction of these plants must be approved by the Department. An extensive laboratory for chemical and microscopical analysis of specimens of water and effluents of sewage-disposal systems is located in the State House and also at the Lawrence Experiment Station, where a bacteriologic laboratory is also maintained and where many systems now used throughout the country for the treatment of water, industrial wastes and domestic sewage have been developed.

This division is also responsible for the abatement of noisome trades, — that is, industries that may cause a nuisance because of odors, — for the control of pollution of streams, ponds and tidal waters, for the supervision and approval of areas for the taking of shellfish and for the operation of shellfish-purification plants and shellfish-handling establishments. This division is also responsible for the general overall supervision of cross-connection between plumbing and sewage-disposal systems.

Biologic Laboratories. The Division of Biologic Laboratories has more than doubled in size in the past two years. Its primary function has been the manufacture of prophylactic and therapeutic biologic products. The Massachusetts Department of Health was the first to make diphtheria antitoxin available for the treatment of diphtheria. We are now adding to our present products the manufacture of whooping-cough vaccine and hope to add tetanus toxoid in the near future. It is the Department's recommendation that every child three months to six months of age should be immunized against whooping cough, and those six months to nine months against diphtheria, and that whenever possible, tetanus toxoid be added in whatever combination with the above two that the physician may desire. The Department expects to manufacture all three products in various combinations for free distribution as soon as personnel becomes available. In addition, the child at about nine months should be vaccinated against smallpox. Ideally, if the family can afford the expense, a booster inoculation of whooping-cough vaccine should be given during the second year of life. Prior to entering school, every child should receive a booster dose of diphtheria and tetanus-toxoid combination and should be revaccinated against smallpox. The Department does not manufacture influenza vaccine and does not recommend its routine use. Typhoid vaccine is now manufactured, and we expect soon to produce the triple typhoid-paratyphoid A and B vaccine for those who may wish its use. The employment of typhoid-paratyphoid vaccine should be limited to groups who are traveling abroad and should not be recommended as routine.

One of the newest activities of the Department is the furnishing of whole blood, plasma, gamma globulin and other fractions of whole blood free of charge to people in communities that have contributed blood on a voluntary basis to the State Blood Program. Because of the limited supply of blood, physicians are urged to select cases for the use of whole blood and blood fractions with care, so that these life-saving products will not be wasted. Supplies are made available first to the families of donors who have contributed during the past year and then to other people in the same community. In an emergency others may obtain these products but not routinely until their community has deposited with the State Blood Program a sufficient amount of blood to ensure that any calls they will make will not overdraw their account. Any physician desiring information regarding the use of any of the prophylactic or therapeutic products may call on the Division of Biologic Laboratories for consultation and advice. The Bacteriology Laboratory, previously located in the State House, and the Serology Laboratory, formerly located at Harvard Medical School, have recently moved to new quarters at 281 South Street, Jamaica Plain. Serology and Bacteriology Laboratories are now essentially merged in quarters adjacent to the Division of Biologic Laboratories.

Tuberculosis and Sanatoria. This division is responsible for the administration of five hospitals and of our tuberculosis program in general. The tuberculosis program may be divided into three main categories. The first comprises diagnostic services, which are available to communities through the outpatient departments, fourteen consultation clinics and three mobile chest x-ray units. We are now making surveys of state institutions, industrial groups and certain selected communities. It is the objective of the Department to make a chest x-ray examination of every person over fourteen years of age within the next five to ten years to disclose active cases, which will be further confirmed by more detailed examinations. Cases that are found to be positive will be hospitalized in sanatoriums so as to afford the patients themselves a better and quicker chance of cure or arrest and to remove, if possible, the danger of infection of their own households and associates. The second aspect of the program has to do with the follow-up study of patients and contacts, including patients who have been discharged from institutions as arrested or against advice.

These must be followed to assure that they will receive the best possible care under the circumstances, that they do not break down, that they are pursuing an occupation that is not a hazard and that they are not a source of infection. The third phase of the tuberculosis program is that of sanatorium care. The Department pays a subsidy of $5.00 per patient to county and municipal sanatoriums, provided they meet the established standards of the Department. At the present time all county and municipal sanatoriums are approved except the Lowell Isolation Hospital. The Department is responsible for the administration of the following institutions:

Rutland State Sanatorium, comprising 365 beds for the care of pulmonary tuberculosis. This was the first state tuberculosis hospital in the country. It should be rebuilt within the Greater Boston area, since it serves primarily the patients from the eastern part of the state.

North Reading State Sanatorium, with 240 beds, of which half are devoted to the care of tuberculosis of children and the other half will be devoted, as soon as personnel is available, to the care of acute rheumatic fever.

Lakeville State Sanatorium, with 304 beds, is devoted primarily to the care of extrapulmonary tuberculosis, such as that of the bones and joints and the kidneys. This institution also has special wards devoted to the care of patients with crippling conditions due to infantile paralysis and spastic paralysis. A limited number of acute cases are also received for hot-pack treatment.

Westfield State Sanatorium, with 189 beds for tuberculosis and 50 for cancer receives cases of pulmonary tuberculosis and cancer and suspected cancer from the western part of the Commonwealth. A large outpatient department will receive any case referred to it either by a private physician or by a welfare organization.

Pondville Hospital, with 145 beds, was the first state cancer hospital established in the United States. A number of new buildings are needed to modernize the institution and to provide adequate living quarters for employees. Approximately six to seven thousand visits are made annually to the out-patient department.

Admission to these sanatoriums is through application made by the private physician and sent to the State House to the Division of Tuberculosis and Sanatoria. Anyone seeking advice about these institutions may call either the State House or the institutions directly.

Communicable Diseases. By law, the attending physician is required to report by name and address to the local board of health every case of disease declared dangerous to the public health. Boards of health furnish proper forms and may seek additional information. The Department of Public Health issues minimum isolation and quarantine regulations, which are enforceable. Local boards of health may have more stringent regulations, but we do not recommend such additions. This division investigates all major cases of communicable diseases with the assistance of the district health officers as well as its own staff. In cases of outbreaks of serious nature, such as food-borne infection or infectious diarrhea of the newborn, a field unit is quickly organized and may call on the assistance of one of the medical schools or the Harvard School of Public Health. A diagnostic laboratory is available to which any physician may send specimens in kits provided by the Department.

This division is prepared to assist physicians in the diagnosis and treatment of more complicated cases of communicable disease. A list of consultants is available to determine the presence or absence of infantile paralysis. Consultants are not available, however, for cases in which paralysis is already present. A list of consultants is published annually in the *New England Journal of Medicine* or may be obtained from district health offices, from the local chapters of the National Foundation for Infantile Paralysis and from local boards of health.

The Division evaluates new immunization procedures, collects and analyzes morbidity and mortality data and issues periodic notices through the column of the Department in the *New England Journal of Medicine* of pertinent information on the incidence and prevalence of communicable diseases in the Commonwealth. Consultant and advisory service is available through its staff and that of our district health offices.

Local Health Administration. This is one of the newest as well as one of the largest divisions in the Department. In it are the bureaus of Public Health Nursing, Nutrition, Sanitary Inspection and Medical Social Work. This division supervises the work of the eight district health offices. The personnel of the district health offices are available as consultants and advisers to the medical and nursing profession and to the local boards of health. They are also available to physicians in the assistance and diagnosis of communicable diseases on problems pertaining to the handling of these cases in general hospitals or in homes. At the request or recommendation of the attending physician the Nursing Bureau of this division will provide nursing care for patients sick in the home, and the Nutrition Bureau will prepare special diets to assist individuals or families with nutrition problems. The Social Service Bureau will furnish information to an attending physician on numerous problems such as adoptions. This bureau also assists physicians in making arrangements for convalescent, nursing or terminal care of patients or for temporary care of children when the mother is hospitalized. District Health Officers have by law certain functions that they must perform, such as inspection of hospitals and other institutions,

the investigation of major cases of communicable diseases, the routine and semiannual check-up on typhoid carriers and the promotion of public health in all the communities of the Commonwealth.

Venereal Diseases. The Division of Venereal Diseases subsidizes twenty-five clinics throughout the State with the co-operation of local boards of health and hospitals. Through these clinics penicillin is made available for the treatment of every case of gonorrhea, syphilis and other venereal diseases. Any patient who cannot afford private treatment may be treated, and transportation to these clinics is also afforded to those unable to pay. The present treatment consists of 2,400,000 units of penicillin over a period of seven and half days, with 0.2 gm. of bismuth subsalicylate given intramuscularly every other day for five doses. Cases of venereal diseases are at present not required to be reported by name. They are reported directly to the Department of Public Health by initial or number. Physicians may report by name if they so desire. Cases that lapse treatment must be reported by name and address for follow-up by workers who are made available through state funds to private physicians in clinics. The law requires that a person desiring to be married must have a serologic blood test performed in an approved laboratory. The Department of Public Health, through the Division of Communicable Diseases, approves laboratories for serologic tests. Persons who have positive tests may marry, but the physician is obliged to inform both parties of the positive reaction and should report the patient to the Department. Physicians are further required to make an examination of the blood of all pregnant women. All specimens may be sent to the Department of Public Health or to approved laboratories. A list of approved laboratories may be obtained from the State House or from the district health offices.

The Department is now experimenting in the treatment of syphilis with penicillin in peanut oil and beeswax. Daily injections of 300,000 units over a period of eight or nine days are given. Preliminary reports on this method of treatment are encouraging.

An attempt is being made to rehabilitate prostitutes and other promiscuous persons. At times, the Department must resort to court action in cases of flagrant violation of the moral code.

Cancer and Other Chronic Diseases. This division is responsible for conducting a cancer-control program and is assisted in the endeavor by the Massachusetts Medical Society and the American Cancer Society (Massachusetts Division), Inc. The program has three objectives: the prevention of cancer; its early recognition and prompt adequate treatment; and studies — biologic, clinical and epidemiologic — to learn more about the disease. The major parts of the program include maintaining a cancer registry, conducting cancer statistical research, furnishing information to both the profession and the laity and service to cancer patients.

Two cancer hospitals, eighteen cancer diagnostic clinics and one contemplated cancer clinic, together with free-tissue diagnosis service to all physicians in the Commonwealth, comprise the service elements of the program. Free service at the clinics is limited to the medically indigent, but experience has shown that relatively few patients are able to pay. Through these clinics and the two hospitals the Department is seeing approximately 10 per cent of all cases of cancer in the Commonwealth.

Education of the public is maintained through local co-operative cancer-control committees, whose chief function is to arrange meetings at which local physicians are invited to speak on cancer. Many thousands of these meetings have been held, and I should like to take this opportunity to thank the physicians of Massachusetts for so freely contributing to this effort.

Specific Services Offered to Physicians

Postgraduate Education

Through funds made available by the United States Public Health Service and the Children's Bureau, the Department can offer physicians postgraduate training in public health. Physicians who have graduated from an approved medical school and who have had one or more years of internship are accepted in the Department in a training position during which they receive a salary of $300 a month for a period of field orientation. Subsequently, if they prove their worth and wish to continue in public health, they may elect to attend any of the ten schools of public health in the United States for an academic year, working toward the degree of master of public health. During their stay at the school, they are paid their tuition, traveling expenses to and from the school, and a stipend equivalent to approximately $300 a month. Physicians who are interested in obtaining such training are expected to pursue careers in public health in the state, local or voluntary health agencies in Massachusetts. Some training is offered to other professional groups. Selected persons may be given a second year of training in public health or in one of the allied fields, provided they expect to work with the state health agency in this field.

With the co-operation of the Massachusetts Medical Society, the Department has been sponsoring postgraduate education of physicians in practice, especially of veterans who have returned after several years of service. Educational facilities have been made available through the postgraduate teaching facilities of the Massachusetts Medical Society, the Sanders Theater programs and, on occasion, special teaching clinics conducted by the Cancer Clinics and special courses devoted to such fields as care of the premature infant, well-child con-

ferences, maternity refresher courses and workshops on infectious diarrhea of the newborn.

The Department furnishes a *Handbook for Physicians*, which has just come off the press and is in the process of being mailed free to every registered physician in Massachusetts. If any of you fail to receive this *Handbook*, please write to the Department requesting it, and it will be mailed to you free of charge. This book contains information regarding not only the services provided by the Department of Public Health but also the legal aspects of medicine in Massachusetts and the follow-up of other services through other governmental departments. Special bulletins, pamphlets and literature are available, both to the public and to the profession, on a variety of subjects, such as tuberculosis, cancer and communicable diseases, as well as reprints of scientific articles and special booklets prepared for the expectant mother and the new mother in the care of her infant and children. A film library containing technical and professional films is available on a loan basis to physicians and medical societies. Speakers on public health and similar subjects are available for services and lay groups within the limits of our personnel. Medical social work and nutrition consultation and the follow-up of patients with venereal diseases who have lapsed treatment are available to the physician on request. Doctors are urged to follow the column of the Department of Public Health that appears in the *New England Journal of Medicine*.

Consultation Services

Consultation services may be offered local doctors, in cases of communicable disease, on diagnosis, specific treatment, immunization and reactions to treatment; on the use of blood, whole blood or blood fractions; tuberculosis; on venereal diseases; on maternal and child health works; on cancer and other chronic diseases; on outbreaks of disease or any local problem; on environmental sanitation; on hospital construction and administration; and on crippled-children's services.

Summary

The Massachusetts Department of Public Health was created largely through the efforts of the Massachusetts Medical Society. Its purpose is to serve the people in the prevention and treatment of disease, the attainment of optimal health and the prolongation of life. These objectives can be attained only by the co-ordinated efforts of all the medical and allied professions, the official state and local health departments and the voluntary health agencies. The Department is convinced that it can best serve the people of Massachusetts by making available to the medical profession the services described so as to enhance the practitioner's facilities in the diagnosis and treatment of disease and in the promotion of good health in his patients.

CARCINOMA OF THE COLON AND RECTUM*

JAMES W. JAMESON, M.D.,† AND CLINTON R. MULLINS, M.D.‡

CONCORD, NEW HAMPSHIRE

THE purpose of this presentation is to give our experience with all the cases of carcinoma of the colon and rectum that have come under our observation from September, 1936, to September, 1946. This experience seems to be of interest since few reports from such small communities as ours (with a population of about 28,000) are forthcoming.

We have tried to follow the most generally accepted methods of management as judged from past experience, observation of procedures in use elsewhere and a study of current literature for improvements in technic and care. We have also attempted to emphasize the importance of nutritional restoration, replacement of vitamin deficiencies, blood transfusions as indicated, fluid balance and careful supervision for complications, both preoperatively and postoperatively. The anesthesia had been almost entirely spinal, either in one dose or fractional, given either by the surgeon and watched by a nurse anesthetist or by a physician who was not a specialist in anesthesia. There have been no serious accidents or failures in this respect. Local anesthesia has been used for preliminary cecostomy when needed.

Sulfaguanidine, sulfasuxidine and sulfathalidine have been used since their introduction, and it is believed that they offer an added factor of safety at operation.

Operative Technic

Catgut sutures have been employed in most cases. Cotton sutures have recently been used, with satisfactory results. Retention sutures of heavy silk or nylon have been placed in most cases but were not used in the 2 cases in which the wounds disrupted; they seem to be a necessary precaution. All anastomoses of the intestine were of the open type, interrupted silk being used for the serosal sutures. It is believed that the added exactness of the open anastomosis more than compensates for the possible danger of contamination. In 24 cases in which this was done there were no deaths and no signs of peritonitis. Local sulfonamide therapy has been employed in all cases of anastomosis — usually 20 per cent microform sulfathiazole suspension in amounts up to 20 cc.

Early ambulation has not been carried out in these cases. There have been no cases, however, showing clinical signs of phlebitis or pulmonary embolism. No case with clinical signs of pneumonia or atelectasis has been observed. Wound infection has not been troublesome.

Carcinoma of the Ascending Colon

There were 14 cases in all, including 12 male and 2 female patients, and of these only 9 cases were considered resectable at operation; in 5 cases that were deemed inoperable because of involvement of other structures and fixation, 1 having a large abscess, palliative procedures were performed. The resections were all done in one stage, in spite of varying degrees of obstruction. There were no postoperative deaths. In the 6 cases in which operation was done three or more years ago, 4 patients, or 66 per cent, are living and well. Of the 2 patients who died, 1 lived seventeen months and succumbed with signs of recurrence and the other lived 10 months. The latter had a cecostomy performed before being seen by us, so that the prognosis seemed poor from the beginning. Of the operations done since 1943, 1 is a recent case, 1 patient is living and well nine months postoperatively, and another died after six months of metastases. The only postoperative complication was infection of the operative wound in 1 case. It seems that carcinoma of the ascending colon presents greater difficulty in diagnosis than any other area for both the roentgenologist and the physician.

The following report is that of a patient in this group who also had a separate lesion in the left transverse colon, which was not discovered until later.

H. R. (C.H. 52512), a 47-year-old woman, was admitted to the hospital on January 26, 1943. She gave a history of rectal bleeding 9 months before admission. She was anemic and received liver and iron for several months before and after that episode. About 2½ months before entry she began to have abdominal cramps and loose stools. A barium enema given shortly before admission showed a lesion of the ascending colon.

The past history was irrelevant.

Physical examination disclosed a pale patient with a firm, slightly tender, movable mass about 9 cm. in diameter in the region of the cecum.

Examination of the urine was negative. Examination of the blood revealed a red-cell count of 4,410,100, with a hemoglobin of 13.1 gm., and a white-cell count of 8600, with 58 per cent neutrophils, 27 per cent lymphocytes, 12 per cent monocytes and 3 per cent eosinophils.

At operation on February 2, the abdomen was explored through a right rectus-muscle-splitting incision. There was a typical growth in the cecum, with no evidence of metastasis to the liver or local lymph nodes. The lesion was easily mobilized and removed, together with the terminal ileum and hepatic flexure of the colon and regional mesentery. An end-to-side ileotransverse anastomosis was carried out.

The pathological report showed a growth 6 cm. in its greatest diameter just distal to the ileocecal valve, involving about half the circumference of the bowel. Microscopical

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†Consulting surgeon, Concord Hospital.

‡Attending surgeon and joint chief of surgery, Concord Hospital.

examination disclosed adenocarcinoma (Grade II) and melanosis coli. No lymph nodes showed tumor.

The convalescence was uneventful, except that the patient remained constipated, the bowels moving only with a laxative or an enema.

Four months later a mass was felt in the left upper quadrant of the abdomen. Abdominal cramps and increasing constipation were also present. A barium enema showed what seemed to be a growth in the left transverse colon near the splenic flexure. At operation on July 17, a typical growth in the left transverse colon was found. There was no evidence of metastasis in the lymph nodes or liver. Resection and end-to-end anastomosis were carried out. The pathological report was adenocarcinoma, with no lymph-node involvement. The convalescence was not complicated, and the patient was discharged on March 8. This patient was still well and free of signs or symptoms of disease in September, 1946.

This case illustrates the importance of searching for multiple lesions both in the x-ray film and at operation.

It is suggested that all cases of unexplained anemia or persistent vague abdominal pain be examined carefully by x-ray with barium by enema and by mouth, the roentgenologist being sure that the entire ascending colon is satisfactorily visualized and not being satisfied with one examination. Also, repeated examinations of the stool for occult blood should be done.

Carcinoma of the Transverse Colon

There were 7 cases in this group, including 5 female and 2 male patients, all but 1 of which occurred three years ago. Resection with anastomosis was done in 5 cases, with no complications, a Mikulicz operation in 1 case, and a palliative cecostomy for obstruction in another. The patients in both the latter cases died after operation; both were acutely obstructed. In the cases of resection and anastomosis, 1 patient is living and well forty-four months and another forty-one months after operation; 1 patient lived thirty-three months and died of recurrence; 1 died of recurrence after eight months; and 1 died of recurrence after three months. Three of these cases required a preliminary cecostomy because of acute obstruction.

Carcinoma of the Descending Colon and Sigmoid

There were 17 cases in this group (8 male and 9 female patients). Five cases had a Mikulicz type of resection; 5 were resected with primary anastomosis; 3 had resection with colostomy, without removal of the rectal stump; 3 had decompression operations only; and operation was not performed in 1. There was 1 death following a palliative operation, but none following resection. There was a postoperative complication in 1 case — an obstruction after closure of a Mikulicz colostomy due to incomplete eradication of the spur; the incision in this case had to be reopened.

Of the patients operated on three or more years ago, 3 are living and well, and the other 3 died of recurrences between five and thirty-five months after operation.

The following case was of more than usual interest.

C. R. (C.H. 48341), a 50-year-old man, was admitted to the hospital on February 17, 1941, because of acute obstruction, with severe crampy abdominal pain and vomiting of 24 hours' duration. There had been no passage of rectal gas for twelve hours. A similar, less severe attack had occurred about 1 month previously, lasting for 2 days. The patient's condition had otherwise been good, except for slight gaseous indigestion. Bowel movements had been regular, with no blood or mucus. There had been no urinary disturbances.

The past history was irrelevant except for a right inguinal hernia of 30 years' duration.

Physical examination revealed fairly marked abdominal distention, with tympany on percussion and excessive peristaltic sounds on auscultation. A large right inguinal hernia, which seemed to be reducible, was present. No growth was felt on rectal examination.

The temperature was 100°F., the pulse 95, and the respirations 22. The blood pressure was 130/80.

The urine showed a trace of albumin and a ++++ test for acetone, and the sediment contained many pus cells, with occasional red cells. Examination of the blood disclosed a white-cell count of 12,600, with 90 per cent neutrophils, 8 per cent lymphocytes and 2 per cent monocytes.

A plain film of the abdomen showed distention of the proximal descending colon but no gas in the rectum. A barium enema demonstrated obstruction in the sigmoid to be complete.

At operation on February 17 a lower right rectus-muscle-splitting incision was made, and the sigmoid growth was palpated and found to be adherent to the anterior abdominal wall. The cecum was greatly distended and tense. A cecostomy was carried out through a McBurney incision.

The patient progressed satisfactorily, and on March 3 the abdomen was opened through a left rectus-muscle-splitting incision. The sigmoid growth was found to be adherent to the anterior abdominal wall and to the dome of the bladder, and dense omental adhesions were observed. The growth was mobilized by dissection, the adherent peritoneum being taken into the pelvis and over the dome of the bladder. The bladder, which could not easily be separated from the growth, was cut across, the entire dome, or almost half the bladder surface, being removed. The defect was closed around a mushroom catheter, which was brought out through the lower angle of the wound. The sigmoid was then divided above and below the growth, and the end brought out as in a Mikulicz colostomy.

Pathological examination revealed adenocarcinoma of the colon and chronic inflammation of the bladder wall.

The convalescence was satisfactory. The suprapubic tube was removed from the bladder after 2 weeks, and satisfactory closure ensued. A crushing clamp was applied to the colostomy spur 2 weeks after operation, and 1 week later the cecostomy was closed under local anesthesia. The patient was discharged on April 13, when the bowels were moving by rectum as well as through the colostomy. On May 28, the colostomy was closed under local anesthesia, the patient being discharged on June 6 with the wound healed.

The patient was followed at frequent intervals and seemed to be well, but 2 years later a fairly hard lump in the lower left-rectus-muscle scar was noted. This was excised on March 10, 1943. The pathological report was scar tissue. A barium enema on March 9 showed no obstruction in the colon at the site of the operation. The patient was still well and free of subjective or objective signs of disease in September, 1946.

Another patient was found to have a growth that completely surrounded the left ureter, a 15-cm. segment of which was removed, the ends being ligated.

Multiple polyps of the colon were subsequently discovered in another case, in which a colectomy with ileosigmoidostomy was performed by Dr.

Richard B. Cattell at the Lahey Clinic. One polyp showed malignant changes.

Also of interest were 2 sisters, who had lesions of the descending colon.

Carcinoma of the Rectum

There were 33 cases in this group, with 19 male and 14 female patients. Abdominoperineal resections were performed in 17 cases — one-stage in 16 and two-stage in 1; in these cases operations were done three or more years ago in 11, and 4 patients (36 per cent) are living and well. There were no postoperative deaths, but serious complications were troublesome. In 1 case the wound disrupted on the fifth day. This patient had liver metastasis at the time of operation. Another disruption occurred on the seventh day, with perforation of the small intestine and extensive soilage from the intestinal contents; repair of the perforation and suture of the abdominal wall were done in bed under local anesthesia, and the patient lived thirty-eight months without recurrence, dying of coronary thrombosis. This patient also had two distinct lesions, one of the rectum and one of the sigmoid.

One patient had a herniation of the small intestine through the pelvic floor, the obstruction being missed at the first operation. This patient was living and well forty-four months after operation. Another also had signs of obstruction postoperatively and was again operated on, but only extensive adhesions were found. The adhesions were considered as possibly due to the sulfathiazole suspension used at the first operation. This patient was well twenty-four months after operation.

There were 2 cases in which only local excision was done. In 1, in which a rectal polyp showed malignant changes, the patient was free of recurrence thirty-five months postoperatively. The other patient had extensive papillary changes, microscopically malignant, and local resection was performed after wide exposure by splitting of the sphincters anteriorly and posteriorly. This patient was free of recurrence and had no incontinence twenty-four months later. Radical operation was refused in this case.

Five cases were treated by radon seeds, 3 for palliative purposes, with little benefit, and 2 for possible cure. One of the latter patients refused surgery, and the general condition of the other seemed too poor for operation. Both had small lesions, which were found to be malignant at biopsy. One was living and well eight years, and the other five and a half years after operation.

Of 2 patients who were not treated, one died twenty-four hours after admission with perforation and peritonitis, and the other was almost moribund on admission.

Summary

Over a ten-year period 71 cases of carcinoma of the colon and rectum were seen. Of these, 49 were deemed to be operable, 4 of which were not treated radically for varying reasons. Forty-five were operated on for cure, with 1 postoperative death — a mortality of 2 per cent. Twenty-eight of this group were treated three or more years ago, and 13 are still living and well — a three-year survival rate of 46 per cent. Of 18 cases seen five or more years ago, 11 were treated for possible cure, and 7 were treated palliatively. Five of the patients treated survived for five years or longer.

The results leave much to be desired but are not wholly discouraging.

Discussion

Dr. Frank H. Lahey (Boston): Three points ought to be stressed in connection with these cases, one of which has not been discussed. The principal one is that this is a favorable lesion, but even the satisfaction derived from the present good results ought not to mislead us regarding another fact that we have stressed again and again: the relation of polyps to cancer, and the need for everyone to think of polyps as possibly precancerous.

Many patients have polyps. No one knows exactly what the incidence is, but it is probably at least 5 per cent. I urge again that every routine physical examination include a proctoscopic and sigmoidoscopic examination, which often discloses polyps that can be removed. It is obvious that not all of them are removed, but, on the other hand, with each polyp that is removed the chances that the patient will have a cancer are reduced.

Proctoscopic examination of colostomies should be carried out after abdominoperineal resection because it is easy to proctoscope a colostomy before the patient goes home. There are definite occasions on which polyps are demonstrated that can be removed, and the patient may well be saved from another carcinoma.

Surgeons are urged to review their personal experiences in operating on patients with carcinoma of the colon and rectum. I know that I have regarded as inoperable cases of carcinoma of the colon or rectum that would be considered operable today in terms of possible cure.

The difference between growth by extension and true metastasis is again stressed. I have in the hospital today a woman who is ready to leave; she had a carcinoma of the rectosigmoid that had perforated into the bladder. She has had a resection of the sigmoid, removal of the left tube and ovary, ligation of the left ureter and resection of two thirds of the bladder.

We used to think that these extensive procedures could not be done, but we have now done combined abdominosacral resections of the rectum, together with total hysterectomy and removal of the tubes and ovaries, in 90 cases. Often, the uterus is involved only by contact extension. Carcinoma of the sigmoid is frequently found on top of the bladder and can be removed by local removal of the portion of the bladder involved, as in this series of cases recorded by Drs. Jameson and Mullins. They illustrate what can be done in relatively small communities if this group of cases can go into a limited number of hands.

We must face facts, even if we do not like them, as I have learned over the years. In the beginning I was not adept at operations on the colon and rectum. It is only by experience that one acquires the ability to handle these late cases — that is, those with contact extensions to the jejunum, those in which the perirenal fat is involved (in which all the perirenal fat can be excised) and those that, by contact, have involved other loops of bowel.

I therefore re-emphasize the facts that these patients who have no other hope, provided they do not have distant metastases and the growth is only local, should all be given much better chances with more radical approaches than

we have often given them in the past, and that many of them will probably enter the group with five-year nonrecurrence rates.

DR. WALTER G. PHIPPEN (Salem, Massachusetts): I know that you are interested in the postoperative morbidity that results from the better preoperative and postoperative care with the use of antibiotic drugs in resection of the colon. Our last 8 cases of resection of the colon are of particular interest.

From December 21, 1945, through September 17, 1946, 8 patients, whose ages ranged from thirty-four to eighty-two years and whose average age was fifty-six years, were operated on. There were 3 cases of carcinoma of the sigmoid, 1 of carcinoma of the rectosigmoid, 1 of carcinoma of the transverse colon, 1 of carcinoma of the descending colon and 1 of obstruction by a fibrofatty mass due to infolding of the wall of the bowel after a resection of a cancer of the ascending colon and ileocolostomy by the Mikulicz technic, as well as 1 case of scar constriction of the sigmoid following a Mikulicz resection of a carcinoma of the sigmoid.

In all cases carcinoma of the large bowel was present or had been present.

The 2 patients in whom the lesions had previously been resected showed no evidence of recurrent disease.

Sulfasuxidine was used in 3 cases, with an abnormal reaction to the drug in 1. Sulfathalidine was used in 5 cases, with no untoward reaction. The dosage for both drugs was the same — namely, 6 gm. a day given in 1-gm. doses at intervals of four hours. Usually, at 10 p.m. the dose was 2 gm., and the 2 a.m. dose was omitted. In the first 5 cases the drug was given for an average of three days before operation, but in the last 3, which have occurred during the past three months, sulfathalidine was given for ten days before surgery was done. The average total preoperative dose was 17 gm. in the first 5 patients, and 62 gm. in the last 3.

In the patient who appeared to be sensitive to sulfasuxidine the drug was given into a defunctioned left colon. On the following day the temperature rose to 103°F., without a corresponding elevation of the pulse or any other signs or symptoms. Two days later the temperature was normal, and the resection was done without further complications. This patient was given 6 gm. of sulfasuxidine a day, by mouth, for two days before closure of the colostomy. She seemed to have no drug fever at that time, but the temperature rose to 102°F. each day for three days after the colostomy had been closed — there was no wound sepsis or other explanation for the fever. This case is the only one of this group in which the temperature rose above 100.6°F. after large-bowel anastomosis by the open technic.

In the patient with carcinoma of the descending colon, a transverse colostomy had previously been performed. In the remaining 7 cases, cecostomy was performed in 5 — in 3 as a complementary procedure, in 1 as an emergency for complete obstruction of the sigmoid and in 1 as a preliminary operation to resection of the transverse colon.

In each case the colon was widely opened and sutured by the open technic. Resection of the bowel was done in each case except the one with obstruction following a Mikulicz right colectomy.

One resection of the sigmoid for scar obstruction was done without proximal vent except that provided by a Harris tube in the small bowel.

Gas was passed by rectum in 7 of the 8 cases in an average of three and a half days after the resection, and a bowel movement by rectum occurred on the average in slightly less than seven and a half days.

All wounds were treated by the method of delayed primary closure, the fascia being closed with interrupted No. 30 cotton suture, and the skin edges being closed by drawing up of the sutures or by clips on the second day. There was no wound sepsis.

CLINICAL NOTE

TUBERCULOSIS IN THE AGED

REPORT OF A CASE

DAVID C. DITMORE, M.D.*

BOSTON

MILLER and Henderson[1] state that one of the greatest deficiencies in tuberculosis control has been the failure to make sufficient use of case-finding technics in the discovery of the elderly person with undiagnosed pulmonary tuberculosis. Meyers[2] believes that the presence of communicable pulmonary tuberculosis in persons over fifty years of age is higher than that in any other age period. The frequency of tuberculosis in the aged has been noted by others.[3–5]

Laird[6] observes that the death rate from tuberculosis per 100,000 population in people over seventy years of age in 1940 was 91 for men and 68 for women and that, since there are 4,250,000 people over seventy years of age in the United States, the total number of deaths is not inconsiderable. Jennings[7] asserts that one of the persistent misconceptions held by the general public about tuberculosis is that it never occurs in older age groups. He claims that even in medical circles the impression is current that old age affords protection against tuberculosis. Of 7212 patients admitted to Glen Lake Sanatorium, however, 13.8 per cent were over fifty years of age[7]; in 1 of these, a woman, the diagnosis was made for the first time at the age of sixty-four. Mariette[8] states that the oldest patient he remembers was a man ninety-four years of age at the time of admission to an institution.

The following case illustrates the necessity of bearing constantly in mind the possibility of tuberculosis in the aged as well as in the young patient. Such cases, when unrecognized, represent a danger to the community.

H. N. M., a 71-year-old man, was referred for examination on December 27, 1946. He stated that until 7 weeks previously he had always been perfectly well. Soreness at defecation had been present since that time, and it had been difficult to keep himself clean because of a discharge from the anus. He denied ever having a temperature, cough, sputum or weight loss.

Examination of the anal canal disclosed the presence of two ulcers. One, located in the anterior commissure, was irregular in outline but measured approximately 1.5 cm. in the widest diameter. The other, which was located on the left posterior lateral quadrant of the anal canal and measured approximately 3 cm. in length and 2 cm. in width, had the appearance of being the result of pressure from a pendulous external hemorrhoid extending across the canal from right to left, the point of contact producing a pressure necrosis.

The edges of both ulcers consisted of a thin layer of skin without evidence of unusual thickening, induration or undermining. The base was covered with small tufts of rather indolent-appearing granulation tissue, which did not bleed easily on trauma. The surface was bathed with a copious grayish-yellow discharge that was easily removed with a

*Instructor, Department of Proctology, Boston University School of Medicine; proctologist, Carney Hospital; consulting proctologist, Brooks Hospital.

cotton-tipped applicator. Because of the unusual appearance of the ulcers, they were excised, and on examination showed changes typically present in tuberculosis. Ordinary treatment for 4 weeks produced no cure of the ulcers, but complete healing occurred 2 weeks after the institution of streptomycin therapy.

On questioning the patient recalled that 2 years previously, while having financial difficulties, he had lost considerable weight, but he had attributed this to worry. He also admitted having a hacking cough in the morning and some sputum, which he thought to be due to an old sinus infection.

A study of the sputum disclosed the presence of many colonies of *Mycobacterium tuberculosis*. X-ray examination of the chest showed a profuse mottling of all lobes of both lungs, having much the appearance of miliary tuberculosis.

References

1. Miller, R. E., and Henderson, B. Undiagnosed pulmonary tuberculosis in elderly persons. *Am. Rev. Tuberc.* **46**:164-171, 1942.
2. Meyers, J. A. Cited by Miller and Henderson.[1]
3. Collis, E. L. Tuberculosis and influenza in relation to World War, 1914–1919, *Tubercle* (Supp.) **21**:3-16, 1940.
4. Freeman, J. T., and Heiken, C. A. Geriatric aspect of pulmonary tuberculosis. *Am. J. M. Sc.* **202**:29-38, 1941.
5. Rich, A. R. Influence of age-determined factors on development of tuberculosis. *Minnesota Med.* **21**:745-763, 1938.
6. Laird, A. T. Tuberculosis in elderly people. *Journal-Lancet* **64**: 208-211, 1944.
7. Jennings, F. L. Tuberculosis among older age groups. *Journal-Lancet* **58**:160-162, 1938.
8. Mariette, E. S., superintendent and medical director, Glen Lake Sanatorium, Oak Terrace, Minnesota. Personal communication.

MEDICAL PROGRESS

"FOLIC ACID": PTEROYLGLUTAMIC ACID AND RELATED SUBSTANCES (Concluded)*

FREDERICK SARGENT, II, M.D.†

CHICAGO

Therapeutic Uses

The diseases in which pteroylglutamic acid has proved to be therapeutically effective are as follows: blood dyscrasias, including Addisonian pernicious anemia (hematologic phase), megaloblastic anemia of infancy, (?) refractory megaloblastic anemia, (?) tropical macrocytic anemia, nutritional neutropenia and nutritional macrocytic anemia, both primary (due to poor diet) and secondary (associated with pregnancy, pellagra, some cases of sprue syndrome, chronic alcoholism, gastric carcinoma and gastric resection); and gastrointestinal disturbances, such as certain cases of tropical and nontropical sprue, chronic diarrhea and celiac disease.

Conditions that have failed to respond to pteroylglutamic acid are certain blood dyscrasias (the neurologic phase of Addisonian pernicious anemia, idiopathic and secondary hypoplastic and aplastic anemia, hypochromic anemia of iron deficiency, anemia associated with cancer, leukemia and lymphoma, leukopenia following x-ray therapy, idiopathic agranulocytosis, agranulocytosis due to sulfonamides, thiouracil, arsenicals, aminopyrine and so forth and idiopathic and symptomatic thrombocytopenic purpura) and gastrointestinal disturbances, including idiopathic ulcerative colitis and certain cases of celiac disease, nontropical sprue and tropical sprue.

Only the more important of these diseases are considered below.

Addisonian Pernicious Anemia

Addisonian pernicious anemia is characterized by a disturbance of hematopoiesis and by combined-system disease. Because these two phases respond differently to therapy with pteroylglutamic acid, each must be considered separately. Many cases of pernicious anemia in hematologic relapse have already been treated with this vitamin, with results that may be summarized as follows. In the peripheral blood, the reticulocytes begin to increase on the fourth to the sixth day, reaching a peak between the seventh and tenth days. The reticulocyte crisis is followed by a gradual rise in the red-cell count and the hemoglobin. In many cases the total white-cell count mounts, and the platelets increase in number. Simultaneously, the bone marrow undergoes a change from the characteristic maturation arrest to a normoblastic picture. A number of investigators have reported that, in spite of prolonged treatment or large doses of pteroylglutamic acid, the reticulocytic crisis is submaximal and the red-cell count and hemoglobin never reach normal values.[28, 39] If such patients are further treated with liver extract, the red-cell count and hemoglobin rapidly reach normal values. Meyer[28] reports that in a few cases small oral doses of pteroylglutamic acid (5 mg. daily), in addition to 0.5 unit of liver extract, often give a reticulocytosis greater than anticipated and that with such therapy the remission is complete. In contrast, Davidson and Girdwood[27] have occasionally achieved excellent hematopoietic responses with as little as 1 mg. of pteroylglutamic acid orally. Along with these hematologic improvements, the patient experiences a feeling of well-being, and the appetite returns to normal. Such symptoms as burning of the tongue, weakness, easy fatigability and dyspnea rapidly disappear.[2, 11, 12, 29]

In contrast to the success in managing the hematologic phase, treatment of the neurologic manifesta-

*Based on a talk presented at a meeting of the Begg Society of Boston University School of Medicine, Boston, on April 7, 1947.

†Formerly, fourth-year student, Boston University School of Medicine.

tions of pernicious anemia has been singularly disappointing. According to most authors pteroylglutamic acid does not cause a neurologic remission or prevent a neurologic relapse. The literature contains an increasing number of reports of patients with early symptoms of combined-system disease that fail to respond to pteroylglutamic acid treatment, with early neurologic manifestations that progress under treatment with pteroylglutamic acid and with no or few early neurologic manifestations who suddenly develop symptoms and signs of advanced disturbance of nervous tissue. These explosive relapses have usually occurred in patients in whom the hematologic phase of the disease has been controlled by pteroylglutamic acid therapy. Table 5 summarizes the available reports on this neurologic relapse. Two points should be brought out: 17 per cent of patients with pernicious anemia treated with pteroylglutamic acid experience, within eight months after the beginning of treatment, either a gradual increase in neurologic manifestations or an explosive and severe neurologic relapse, most of the cases in these series undergoing the latter type of neurologic disturbance; and in cases developing the severe neurologic manifestations, the posterior columns uniformly tend to be extensively involved, the lateral columns being much less frequently and severely involved.

TABLE 5. *Neurologic Involvement in Patients Treated with Pteroylglutamic Acid Who Had No Neurologic Involvement at Beginning of Treatment.*

AUTHOR	TOTAL NO. OF CASES	CASES DEVELOPING SIGNS		ONSET OF SIGNS AFTER TREATMENT	CASES WITH RAPID AND SEVERE INVOLVEMENT	SITE OF INVOLVEMENT IN SEVERE CASES		
		NO.	PERCENTAGE	*mo.*		PERIPHERAL NERVES	POSTERIOR COLUMNS	LATERAL COLUMNS
Vilter et al.[40]	24	5	21	2–8	2	2	2	1
Heinle and Welch[34]	47	3	6	?	1*	1	1	?
Meyer[28]	11	3*	27	1½–3	3	3	3	?1
Hall[41]	14	5	36	?	?	?	?	?
Castle and Berk[37]	5	1	20	11	1	1	1	0

*Symptoms and signs, which were present at the start of treatment, progressed and rapidly became severe.

How are these observations to be interpreted? Because on the one hand, the hematologic phase of this disease responds to treatment with pteroylglutamic acid whereas, on the other, the neurologic phase fails to respond, pernicious anemia is probably a multiple-deficiency disease. Furthermore, it appears — as pointed out by Heinle and Welch[34] — that treatment of pernicious anemia with pteroylglutamic acid frequently precipitates, and indeed may even cause, the neurologic manifestations, usually occurring after hematologic remission, and that these may not be identical with the syndrome called "combined-system disease." Combined-system disease is characterized by the insidious onset of signs and symptoms attributable to degenerative changes in the peripheral nervous system and in the posterior and lateral columns of the central nervous system. The neurologic manifestations may precede the onset of anemia, and in the majority of cases these symptoms are not correlated with the degree of anemia. The neurologic manifestations that occur in patients treated with pteroylglutamic acid have a relatively rapid onset — in many cases, actually explosive — and the symptoms and signs in these rapid and severe cases are referable to disturbance principally in the posterior columns. If it is granted that pernicious anemia is due to a deficiency of more than one substance, one of which is pteroylglutamic acid, may it not be concluded that correction of part of the deficiency accentuates the manifestations of the remainder of the deficiency? Such a situation often results in the course of treating a multiple avitaminosis with a single vitamin. Pteroylglutamic acid is the factor essential for the continuation of normoblastic blood formation.[27] Because purified liver extract prevents or in part corrects the neurologic manifestations, such extracts must contain one or more substances essential for the maintenance of nervous tissue.

The case for the use of pteroylglutamic acid in Addisonian pernicious anemia is by no means closed, for it may turn out that in combination with liver therapy a more satisfactory management may be achieved. In any case, the use of pteroylglutamic acid alone in the treatment of these cases is not at present recommended.

The entry of a new therapeutic agent into the realm of medicaments naturally requires brief consideration of the relation between this substance and liver extract. In the process of purification pteroylglutamic acid is removed from the extract so that the final purified preparation contains only traces of this vitamin — an amount far less than that which is therapeutically effective. Pteroylglutamic acid, in contrast to liver extract, is equally effective orally and parenterally. Furthermore, this vitamin, unlike liver extract, fails to control the neurologic phase of pernicious anemia. It is apparent, then, that pteroylglutamic acid is not the principle in liver extract effective in pernicious anemia. Nor is it the extrinsic or the intrinsic

factor described by Castle. In addition, there is no anemia relieved by pteroylglutamic acid that does not also respond to therapy with liver extract.[42] These points comprise a list of disadvantages against the pteroylglutamic acid as the "new hope for anemic patients." Do any advantages accrue from the use of this vitamin? Two features have been suggested: oral therapy obviates repeated injections, but weighed against the possibility of neurologic relapse, this can scarcely be considered an advantage; and pteroylglutamic acid may be employed when patients are allergic to liver extract.[42] Against the latter consideration is the fact that patients allergic to pork-liver extract react satisfactorily to beef-liver extract given parenterally.[43]

Blood Dyscrasias of Nutritional Origin

The megaloblastic anemias of nutritional origin that respond to pteroylglutamic acid may be due either primarily to a poor diet or to secondary nutritive failure consequent to anorexia, poor absorption and utilization or increased requirements. The secondary cases are seen in such conditions as pellagra, pregnancy, the sprue syndrome, chronic alcoholism and gastric carcinoma. In cases of sprue, as pointed out below, the hematopoietic disturbance frequently fails to respond to therapy with pteroylglutamic acid. When neutropenia or thrombocytopenia occurs as a manifestation of nutritive failure, an increase in leukocytes and platelets will follow the administration of pteroylglutamic acid. If, however, the anemia is normoblastic or hypochromic (due to an iron deficiency) and the neutropenia and thrombocytopenia are idiopathic or secondary, administration of this nutrient effects no hematologic response.

Refractory Megaloblastic Anemia

Some cases of macrocytic anemia that present blood and bone-marrow pictures indistinguishable from pernicious anemia have no achlorhydria and fail to respond to parenteral purified liver extract. Such cases, however, respond to administration of crude extracts and yeast. These cases, which are called "refractory megaloblastic anemia," probably arise from poor dietary habits. Wills and her associates[44, 45] have described such cases from India, suggesting that the name "tropical macrocytic anemia" be used to designate the condition. Wills[46] has produced a macrocytic anemia with a megaloblastic marrow in monkeys by the administration of a poor diet similar to that eaten by human patients with tropical macrocytic anemia. This monkey anemia is refractory to parenteral purified liver, but responds to a relatively purified substance from yeast preparations. Watson and Castle[47] suggest that this factor be called the Wills factor. The relations between the Wills factor and pteroylglutamic acid or between Wills monkey anemia and vitamin M deficiency have not been established, but some workers have assumed that the two substances — pteroylglutamic acid and the Wills factor — are closely related, if not identical.[3]

One test of the relation between these substances is whether or not refractory megaloblastic anemia will respond to the administration of pteroylglutamic acid. Some cases called "refractory megaloblastic anemia" have been successfully treated with pteroylglutamic acid, but the criteria for so designating these particular cases is not clear. Two cases in this series seemed to fulfill the criteria for a diagnosis of refractory megaloblastic anemia. The patients showed a partial hematologic response to pteroylglutamic acid and were completely cured by further treatment with crude liver extract. One patient had a marked reticulocytosis on two occasions three weeks apart after treatment with purified liver extract, although there was no appreciable change in the red-cell count or the hemoglobin.[27] One wonders if this case might not also have responded to purified liver extract if more than two injections had been tried. The results of this study suggest, however, that the Wills factor and pteroylglutamic acid are not identical.

Aplastic Anemia

Although most authors[2, 27, 29] report that aplastic anemia does not respond to pteroylglutamic acid, a few long-standing cases have shown variable but incomplete remissions following prolonged treatment with massive doses of pteroylglutamic acid.[48] The possibility that these patients were not merely undergoing spontaneous remissions was not satisfactorily ruled out.

Sprue Syndrome

The sprue syndrome consists of celiac disease in children and tropical and nontropical sprue in adults. There are a variety of reports in the literature concerning the response of this syndrome to pteroylglutamic acid.

Six cases of celiac disease have been treated with pteroylglutamic acid. In 3, a megaloblastic anemia accompanied the gastrointestinal disturbance. These cases have been reported only in summary, but they apparently responded with rapid clinical and hematologic improvement.[49, 50] Three other patients with hypochromic anemia were not benefited by pteroylglutamic acid.[51]

In the cases of nontropical and tropical sprue, there is likewise wide divergence of opinion regarding the usefulness of pteroylglutamic acid. So far as the associated anemia is concerned, some investigators[16, 23, 29, 38, 52–54] report striking improvement, whereas others[51, 54, 55] report no improvement. Part of the variation in response seems to be due to the degree of anemia at the beginning of treatment with pteroylglutamic acid. This vitamin fails to effect a complete remission of the anemia. If the anemia is severe, there will be striking improvement, but the

remission will be incomplete. If the anemia is only moderate (a red-cell count of about 4,000,000) there may be no response. These results suggest that in some cases of the sprue syndrome there is a deficiency of the Wills factor, as well as of pteroylglutamic acid. Many authors[16, 23, 29, 38, 51–54] report that the clinical improvement in cases of tropical and nontropical sprue is remarkable and dramatic. There is rapid restoration of appetite and sense of well-being. Epigastric distress disappears. More slowly, the body weight is restored to normal. Some cases fail to respond permanently, although they may show temporary improvement.[55]

Together with clinical improvement, there is marked improvement in gastrointestinal function. The bowel movements decrease in number and become normal in odor, color and consistence. The gastrointestinal mucosa is restored to its normal condition. Davidson and Girdwood[51] point out that in their series of 7 cases the most remarkable improvement of intestinal function occurred about the fifth day after the beginning of treatment with pteroylglutamic acid.

Metabolic improvement has also been noted by some workers. The blood levels of carotene and vitamins A and E are increased.[7] Some workers[7, 38] have reported restoration of glucose tolerance to normal. Others[51] have been unable to detect much change in fat absorption.

Further clinical study will be required before a final evaluation of the place of pteroylglutamic acid in the management of the sprue syndrome can be made. The hematologic results suggest that some other substances are necessary for a complete remission. The complicating roles of intestinal infestation with bacteria and parasites and of poor nutrition have not been adequately studied. A recent report by Suárez et al.[38] emphasizes the fact that the response of this syndrome to pteroylglutamic acid may be facilitated by an accompanying adequate diet.

Other Gastrointestinal Disturbances

Carruthers[19] reports that 6 cases of chronic diarrhea of six weeks' to six months' duration of diverse etiology responded promptly to pteroylglutamic acid. All these patients had failed to respond to specific or symptomatic treatment. When 40 to 60 mg. of pteroylglutamic acid had been given daily by mouth for two to five days, the diarrhea rapidly cleared, and there was general clinical improvement. The author suggests that a nutritional factor probably prolonged the abnormal stools.

Five cases of idiopathic ulcerative colitis have been treated unsuccessfully with pteroylglutamic acid.[27] Two of the patients apparently became worse during the course of therapy.

Cancer

From the experimental laboratory comes suggestive evidence that pteroylglutamic acid and related substances play a role in the growth of neoplastic tissue. Lewisohn and his associates[56] have shown that, in spontaneous breast cancer in mice, pteroyltriglutamic acid (fermentation *L. casei* factor) given intravenously daily in doses of 5 mg. for four to six weeks caused complete regression of the neoplastic growth in about a third of the test animals. Pteroylglutamic acid (liver *L. casei* factor) in doses of 5 and 100 mg. intravenously did not cause appreciable regression of neoplastic tissue. In fact, as compared with the controls, the incidence of lung metastases seemed greater. Perhaps other pteroylpolyglutamic acids that will prove efficacious in the treatment of human cancer will be synthesized.

Summary

A review of the current literature reveals that the newest member of the vitamin B complex — popularly called "folic acid" — may prove effective in the management of a variety of blood disorders and certain abnormal gastrointestinal conditions.

This vitamin has been isolated and synthesized. Its chemical name is pteroylglutamic acid. Pteroylglutamic acid is identical with the *Lactobacillus casei* factor necessary for growth of *L. casei*, vitamin B_c necessary for growth and hematopoiesis in the chick and vitamin M, which prevents cytopenia and a fatal sprue-like syndrome in monkeys. The related substances, pteroic acid and pteroyltriglutamic acid (the active principle in fermentation *L. casei* factor), have been synthesized. The active material in the vitamin B_c conjugate (or "folic acid" conjugate) has been identified as pteroylheptaglutamic acid, but this heptapeptide has not yet been synthesized. A compound containing thirteen molecules of glutamic acid has also been isolated from yeast.

An enzyme that hydrolyzes the tripeptides and heptapeptides to glutamic as well as pteroylglutamic acid has been discovered. This enzyme, known as vitamin B_c conjugase, is abundant in such animal tissues as liver, kidney, pancreas and bone marrow.

Foods have been found to contain an unidentified substance — conjugase inhibitor — that impedes the hydrolytic activity of the enzyme vitamin B_c conjugase.

Pteroylglutamic acid is widely distributed in nature but the amount present even in the best sources, such as spinach and liver, is only of the order of 100 microgm. per 100 gm. The amount of pteroylglutamic acid in the ordinary diet is far less than that which is therapeutically effective. Until the nutritional requirements for this vitamin are known, however, a final evaluation of the richness of the nutrient in nature cannot be made.

Most of the naturally occurring vitamin is present as pteroylheptaglutamic acid.

The important deficiency symptoms due to lack of this essential nutrient are failure of growth, cytologic disturbances and gastrointestinal disorders. The mode of action of pteroylglutamic acid is unknown, but it has been shown that although the heptapeptide is not efficiently utilized by patients with Addisonian pernicious anemia, pteroylglutamic acid can be utilized to some extent. The inability to make use of the heptapeptide is apparently due to failure to neutralize conjugase inhibitor.

Pteroylglutamic acid is nontoxic for animals and is without toxic effect in large doses given orally or intramuscularly to man. Intravenous administration to human patients, however, is not recommended because of several cases of shock-like reaction that have followed when this route has been used.

The currently recommended therapeutic dosage is 10 mg. orally each day. For maintenance 5 to 10 mg. daily has been found effective in most cases.

Pteroylglutamic acid has proved effective in the treatment of a variety of blood dyscrasias, including Addisonian pernicious anemia, nutritional macrocytic anemia and neutropenia, macrocytic anemias of infancy and pregnancy and macrocytic anemias following gastric resection. The evidence for the response of refractory megaloblastic anemia to pteroylglutamic acid is still incomplete. An occasional case of aplastic anemia may respond to this vitamin.

There is no anemia that responds to pteroylglutamic acid that does not also respond to liver extract.

Pteroylglutamic acid does not cause a neurologic remission, nor does it prevent a neurologic relapse among patients with Addisonian pernicious anemia. Indeed, in some cases it seems to precipitate or cause a sudden outbreak of symptoms and signs due to predominant disturbance in the posterior columns. For these reasons, management of Addisonian pernicious anemia with pteroylglutamic acid is not recommended.

Pteroylglutamic acid has no place in the management of hypochromic anemia due to iron deficiency; anemias associated with cancer, leukemia and lymphomas; and idiopathic and secondary (symptomatic) hypoplastic anemia, aplastic anemia, agranulocytosis and thrombocytopenic purpura.

Evaluation of the effectiveness of pteroylglutamic acid in the treatment of the sprue syndrome is difficult, for different investigators have reported both successes and failures. More exact definition of the clinical entities being studied is probably needed.

Some cases of "chronic diarrhea" due to nutritive failure are benefited by pteroylglutamic acid.

No benefit accrues from the use of this nutrient in idiopathic ulcerative colitis. In fact, some patients seem to be made worse by such treatment.

Because fundamental knowledge concerning the action of pteroylglutamic acid is still limited and because a full clinical trial has not been made, it is too early to venture an opinion on the final place of this nutrient in therapeutics.

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Presbyterian Hospital

References

39. Tuttle, M. J., and Scott, J. W. Folic acid in treatment of pernicious anaemia. *Canad. M. A. J.* **56**:396-400, 1947.
40. Vilter, C. F., Vilter, R. W., and Spies, T. D. Treatment of pernicious anemia and related anemias with synthetic folic acid. I. Observations on maintenance of normal hematologic status and on occurrence of combined system disease at end of one year. *J. Lab. & Clin. Med.* **32**:262-273, 1947.
41. Hall, B. E. Discussion of papers on folic acid read at Nineteenth Annual Meeting of Central Society for Clinical Research. *J. Lab. & Clin. Med.* **32**:338-340, 1947.
42. Editorial. Folic acid. *New Eng. J. Med.* **236**:219, 1947.
43. Bauer, J. L., Watson, R. J., Chambliss, J. R., and Davidson, C. S. Sensitivity to pork-liver extract in pernicious anemia: clinical observations on fourteen patients. *New Eng. J. Med.* **236**:622-625, 1947.
44. Wills, L., and Evans, B. D. F. Tropical macrocytic anaemia: its relation to pernicious anaemia. *Lancet* **2**:416-421, 1938.
45. Wills, L. Treatment of "pernicious anaemia of pregnancy" and "tropical anaemia," with special reference to yeast extract as curative agent. *Brit. M. J.* **1**:1059-1064, 1931.
46. Wills, L., Clutterbuck, P. W., and Evans, B. D. F. New factor in production and cure of macrocytic anaemias and its relation to other haematopoietic principles curative in pernicious anaemia. *Biochem. J.* **31**:2136-2147, 1937.
47. Watson, J., and Castle, W. B. Nutritional macrocytic anemia, especially in pregnancy: response to substance in liver other than that effective in pernicious anemia. *Am. J. M. Sc.* **211**:513-530, 1946.
48. Gendel, B. R. Folic acid in treatment of aplastic anemia. *J. Lab. & Clin. Med.* **32**:139-146, 1947.
49. Brody, H. P., and Gore, L. Folic acid in coeliac disease. *Lancet* **2**: 618, 1946.
50. Dalton, H. W., Thomson, M. L., and Wilson, V. K. Folic acid in coeliac disease. *Lancet* **2**:652, 1946.
51. Davidson, L. S. P., Girdwood, R. H., and Innes, E. M. Folic acid in treatment of sprue syndrome. *Lancet* **1**:511-515, 1947.
52. Darby, W. J., Jones, E., and Johnson, H. C. Use of synthetic *L. casei* factor in treatment of sprue. *Science* **103**:108, 1946.
53. Manson-Bahr, P., and Clarke, O. Folic acid in tropical sprue. *Lancet* **2**:903, 1946.
54. Morrison, R. J. G., and St. Johnston, C. R. Treatment of tropical sprue with folic acid. *Lancet* **1**:636, 1947.
55. Comfort, M. W. Discussion of papers on folic acid read at Nineteenth Annual Meeting of Central Society for Clinical Research. *J. Lab. & Clin. Med.* **32**:338-340, 1947.
56. Lewisohn, R., Leuchtenberger, C., Leuchtenberger, R., and Keresztesy, J. C. Influence of liver *L. casei* factor on spontaneous breast cancer in mice. *Science* **104**:436, 1946.

Additional References

Dacie, J. V., and White, J. C. Folic acid in sprue syndrome. *Lancet* **1**: 614, 1947.

Editorial. Folic acid. *Brit. M. J.* **1**:604, 1947.

Spies, T. D., Vilter, C. F., Cline, J. K., and Frommeyer, W. B., Jr. Substitution of thymine for folic acid in treatment of macrocytic anemias in relapse. *South. M. J.* **39**:269, 1946.

Vilter, C. F., Vilter, R. W., and Spies, T. D. Occurrence of combined system disease in persons with pernicious anemia during treatment with the *Lactobacillus casei* factor (folic acid). *J. Lab. & Clin. Med.* **32**:335, 1947.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 33451

PRESENTATION OF CASE

A seventy-six-year-old woman was admitted to the hospital because of abdominal pain.

For three years the patient had attacks of pain in the right lower quadrant of the abdomen, lasting only a few hours and associated with some constipation during these attacks. Eight days before admission, while riding in a car, she had a brief attack of pain, and finally, three days later, the pain became persistent. It radiated from the right lower quadrant to the back and to the left side of the abdomen but was not crampy in character. It was associated with nausea and vomiting of all solid food. There was no bowel movement in this interval, but she was able to pass gas.

The past illnesses and operations included an appendectomy thirty-five years before entry, a left salpingo-oophorectomy before entry, thyroidectomy twenty years before entry and a coronary thrombosis nine years before entry. She had had a Parkinsonian tumor for years. She had anginal attacks and had recently been taking digitalis.

Physical examination revealed a well nourished, dehydrated woman with a Parkinsonian tremor of the left arm and leg. The heart was enlarged, the border of cardiac dullness extending to the left. The whole abdomen was tender, especially in the right lower quadrant, where there was an exquisitely tender palpable mass measuring about 9 cm. in diameter. This mass was also palpated in the right fornix on pelvic examination. Peristalsis was normal.

The temperature was 98°F., the pulse 95, and the respirations 22. The blood pressure was 250 systolic, 120 diastolic.

Examination of the blood disclosed a hemoglobin of 16 gm. and a white-cell count of 11,400, with 86 per cent neutrophils. The nonprotein nitrogen was 47 mg., the fasting blood sugar 112 mg. per cent, the total protein 6.5 gm. per 100 cc., and the chloride 89 milliequiv. per liter. A routine urine examination was negative.

A plain film of the abdomen showed gas-filled loops of small and large bowel. No gas was seen in the left colon distal to the hepatic flexure.

An operation was performed six hours after admission.

DIFFERENTIAL DIAGNOSIS

DR. MARSHALL K. BARTLETT: May we see the x-ray films?

DR. STANLEY M. WYMAN: The gas-filled colon described is seen extending from the region of the cecum to the splenic flexure. I cannot trace it with certainty below that point. There is some gas in the small bowel, but the bowel does not appear dilated. There are no areas of unusual calcification. I cannot outline the mass that is described.

DR. BARTLETT: I was hoping for more help but must proceed with what is given. This patient was seventy-six years old and had a past history of two laparotomies and, in the past three years, attacks of pain in the right lower quadrant, usually lasting only a short time. The attack that brought her to the hospital lasted for five days, and the pain was described as always being in the right lower quadrant with radiation to the back and left side. It was not crampy, but had been associated with vomiting. What processes would cause that picture, together with the physical finding of an exquisitely tender mass palpable in the right lower quadrant and also felt by pelvic examination? Of course the first thing that comes to mind in a person with previous abdominal surgery is intestinal obstruction. Favoring that is the fact that she had not had a bowel movement for five days, although she had been able to pass gas during that period. To explain the mass we must assume that she had a loop of bowel that in some way became incarcerated or strangulated. It seems to me that at the end of five days with a situation of that kind there would have been more x-ray evidence of dilated small bowel than we have. I do not see how we can explain this picture of intestinal obstruction on the basis of something in the colon. Because of the situation in the right lower quadrant it would have to be something in the cecum presumably. Certainly, from the x-ray picture there was more gas in the right colon than elsewhere in the bowel. I therefore do not believe that this case will fit that picture.

What else could it have been? The appendix has been ruled out because it had been removed. There is the technical possibility of a residual section of appendix that developed into an abscess, but I cannot quite picture this as an abscess in the right lower quadrant. The normal temperature and moderate elevation of the white-cell count seem to me rather against something that had perforated and formed an abscess. Another fairly remote possibility is a Meckel's diverticulum. If it were diverticulitis of the sigmoid it would be more likely to be on the other side. A single diverticulum of the cecum is occasionally seen but is certainly rare, and again one would have to assume that it started with an acute inflammatory process with perforation and

abscess formation. I think that the picture would have been a little different if this had been an abscess from any source.

Regional enteritis must be thought of, but there is no particular feature of the history to point in that direction. I suppose that in that condition a palpable mass can be formed, but I do not believe that it would have been of the type described in this case unless, again, it had perforated, with abscess formation.

How about the pelvis as a source of this patient's problem? The left tube and ovary had been removed for a condition the nature of which we do not know. To the best of our knowledge the right tube and ovary and the uterus were still present. Nothing is said in the history about the menstrual cycle. We can assume, however, that the menopause had occurred many years previously. It seems to me that an ovarian cyst is a definite possibility. At her age that is more likely than a fibroid with a twisted pedicle. I therefore believe the diagnosis of a twisted cyst best explains the sudden onset, the presence of an exquisitely tender mass at the end of five days, the normal temperature and the moderate elevation of the white-cell count.

Clinical Diagnosis

Twisted ovarian cyst.

Dr. Bartlett's Diagnosis

Ovarian cyst, with twisted pedicle.

Anatomical Diagnoses

Carcinoids of ileum, with metastasis to mesenteric lymph nodes.
Volvulus of ileum.

Pathological Discussion

Dr. Francis Ingersoll: My preoperative diagnosis was a twisted ovarian cyst. When the abdomen was opened a gangrenous loop of small bowel presented. On the mesenteric border of the bowel there was a hard area, and deep in the mesentery of the bowel there was a similar hard mass. Farther up in the ileum there was a small nodule in the bowel wall. The bowel was infarcted because of a three-quarter turn at the level of the mass in the mesentery. Inspection of the ovaries and exploration of the abdomen failed to show any evidence of cancer or evidence of anything that might be connected with the two nodules previously mentioned. Three feet of gangrenous terminal ileum were resected, and a side-to-side anastomosis between ileum and cecum was performed.

Dr. Benjamin Castleman: The specimen we received was a loop of bowel, about 90 cm. long, the middle third of which was thickened and gangrenous. This gangrenous loop was twisted and adherent around an infiltrating mesenteric mass. On opening the bowel we found in the region of the interadherence a submucosal tumor about 2.5 cm. in diameter invading the wall of the bowel, but there was a definite space between the mesenteric mass and this nodule. We noted a smaller but similar nodule about 25 cm. away from the first nodule.

Microscopical examination of these two tumors showed them to be argentiffinomas or carcinoids, and the mesenteric mass proved to be a metastasis from one of the tumors. The carcinoid of the small bowel is a slowly growing tumor, and this one must have been present for years, finally metastasizing to one of the regional nodes. It was the mesenteric metastasis that had produced the adherence and the volvulus. Dr. Ingersoll, will you describe the course following operation?

Dr. Ingersoll: The patient was an elderly woman, and we were pleased for the next ten days that the progress was satisfactory. During that time she passed a little gas and had a moderate amount of drainage from the nasal tube, and we thought that she was over the worst part of the illness. On the eighth and ninth days, however, she was nauseated and passed gas and watery movements by rectum. On the eleventh day she was again nauseated. Physical examination revealed active peristalsis, but there was a mass in the right upper quadrant. This mass seemed to be connected with the liver. It was quite discrete and very easy to feel. There was no spasm except over the mass, and the rest of the abdomen was soft and nontender. She was jaundiced. It was apparent that she was a desperately ill woman, and that nothing further surgically could be done at that time. She was given supportive therapy and had a shaking chill in the afternoon and another in the evening. At 4 in the afternoon she was quite deeply jaundiced, and the pulse, which had been 88 in the morning, was 130, and the temperature was 105°F. The house officers were called late that night and said that she was more deeply jaundiced than she had been at 6 or 7 in the evening, when I had seen her. She died early in the morning.

Dr. Castleman: Autopsy showed an acute condition of the gall bladder, which was distended, markedly injected and covered with fibrin. A small stone, 1 cm. above the ampulla of Vater in the common bile duct, was completely obstructing the lumen. No other stones were found in the bile ducts or gall bladder. The liver was enlarged and deep green.

CASE 33452

Presentation of Case

A seventy-two-year-old Negro entered the hospital because of swelling in the neck.

Seven months before admission a swelling in the neck had been noted in the Out Patient Department of a neighboring hospital, and since that time the patient had observed that it did not change

appreciably in size. There had been no difficulty in breathing or swallowing and no toxic symptoms. He had lost 30 pounds in weight during the year prior to admission. Scoliosis of the spine had been present all his life and had become somewhat worse during the few years prior to admission. Twenty-one years before admission cough, weakness, weight loss and chest pain were noted, and a diagnosis of tuberculosis was made. Treatment consisted of rest at home, and apparent recovery ensued. There had been no hemoptysis and no recent cough. During the two months before admission he had been bothered by dyspnea and left precordial pain on exertion. There was no ankle swelling.

The patient admitted to having had gonorrhea in his youth and during the three years before admission suffered from urinary hesitancy and a weak stream. A year after the onset of these complaints a sinus appeared in the perineum, which drained pus but never urine or fecal material. This never actually bothered him until three months before admission, when he noted the onset of frequency of urination associated with considerable perineal pain. There was also pain on moving the bowels. For two weeks before admission he had been bothered by marked anorexia and occasional attacks of "dry heaves." He admitted to having always liked cabbage and to having eaten much of it all his life.

Physical examination showed a well developed but emaciated man. The thyroid gland was diffusely enlarged to about four times the normal size, moderately firm and nontender. No bruit was heard. The spine showed moderate scoliosis, with convexity to the right in the dorsal region and to the left in the lumbar region. There were dullness, decreased breath sounds and tubular breathing over the left apex and a high diaphragm without movement on the left side. Over the right apex the breath sounds had a tubular quality, and whispered voice was increased. The heart was enlarged to percussion; the sounds were of fair quality, and there were occasional premature beats with compensatory pause and no pulse deficit but notable variation in force of beat. No murmurs were heard. There was moderate costovertebral-angle tenderness. The right testicle was atrophic, and the cord was thickened. There was a sinus at the perineoscrotal angle. Rectal examination was unsatisfactory because of extreme generalized tenderness.

The temperature was 99°F., the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

The urine showed a ++++ test for albumin and contained innumerable white cells. The hemoglobin was 98 gm. per 100 cc., and the white-cell count 19,500, with 81 per cent neutrophils. The nonprotein nitrogen was 70 mg. per 100 cc. A smear from the perineal sinus was negative for acid-fast bacilli. Urine cultures revealed abundant colon bacilli and nonhemolytic streptococci. Smears showed no tubercle bacilli.

An x-ray film of the chest disclosed marked kyphoscoliosis. The left leaf of the diaphragm and the left border of the heart could not be traced, and only a few cystic areas of lung could be seen on the left side. The right lung showed mottled areas of increased density scattered throughout all lung fields, particularly at the apex. The hospital course was febrile, with temperatures as high as 102.5°F. and with white-cell counts as high as 38,000. Catheterization revealed 3000 cc. of residual urine; the urethra was dilated, and a Foley catheter inserted. Digital examination on the third hospital day ruptured a perirectal abscess into the rectum. On the fifth hospital day the patient was found to be cold, clammy and unresponsive. The pulse was 130, the respirations 40 and grunting, and the blood pressure 80 systolic, 20 diastolic. He died later on the same day.

Differential Diagnosis

Dr. Earle M. Chapman: May we see the x-ray films?

Dr. Stanley M. Wyman: It is impossible to outline the left leaf of the diaphragm. I cannot describe the heart, which is inadequately defined. The left side of the chest contains numerous, rather thick-walled, cyst-like areas, with no obvious fluid in the rounded areas. The possibility of a herniation of colon into the chest might be mentioned in passing. I do not consider that very likely, however. This is the scoliotic spine, with kyphosis also apparent in the lateral view. Throughout the right lung there is mottled density, which is rather concentrated at the apex. The density is somewhat linear but also rather soft and mottled in the lower two thirds of the lung field. I believe that this is old chronic disease in the left side of the chest. What is going on in the right side is hard to say.

Dr. Chapman: Does it look like active tuberculosis to you?

Dr. Wyman: It might be a bronchial spread or, less likely, a miliary spread of tuberculosis, although it does not look typical of the latter. I do not see cavity formation, but cavities might be concealed in the right apex.

Dr. Chapman: The physical findings were suggestive of cavitation.

Dr. Wyman: In this view the rarefaction can be seen. It could be cavitation.

Dr. Chapman: Do you think that that is cystic disease of the lung on the left?

Dr. Wyman: Yes; it might be due to a sclerosing process, possibly tuberculous, with bronchial involvement.

Dr. Chapman: The mechanical factor compressing the left lung must be considered. We know that patients with severe scoliosis sometimes de-

velop emphysematous blebs as an attempt at compensation.

DR. WYMAN: I think that this is more than emphysema. These are thick-walled, cyst-like areas in the lung, not thin-walled emphysematous blebs. Perhaps in keeping with that is the suggestion of thickening of the pleura along the lateral chest wall.

DR. CHAPMAN: It is not surprising that there was severe dyspnea. Evidently, the vital capacity was not determined, but I assume that it was markedly reduced. This man had known tuberculosis, and toward the end he must have had bilateral extensive tuberculosis with cavitation and with perhaps more recent spread on the right. An interesting clinical point in patients with this degree of tuberculosis is that they have dyspnea out of proportion to the signs on examination. The history is compatible with that diagnosis, but there was something else going on — that is, a perirectal abscess, which was drained. In addition, the urine contained a great deal of albumin, and there were signs of uremia. The question arises, Was this on an obstructive basis from the perirectal abscess, or, in the face of this long-standing disease, did the patient have amyloid disease of the kidney? Little or nothing about renal function is indicated. It is stated that there was tenderness in the costovertebral angle and retention of urine, with 300 cc. of residual urine, and that the patient was in uremia. I do not see how it is possible to establish which of these two possibilities was present, but we must consider the possibility of amyloid disease of the kidney.

Then we come to the matter of thyroid disease, because of this mass in the neck, and I assume that that is why I was asked to discuss this case. The patient first came to the hospital because of swelling of the neck, and a goiter could be felt that was about four times the size of a normal thyroid gland and was moderately firm and nontender.

I wondered about thyroid hyperplasia, but there is no evidence in this record of symptoms or signs of hyperthyroidism, so that we can exclude that diagnosis. With all this tuberculosis in the body, — at least I assume it to have been that, — was this tuberculosis of the thyroid gland? That is extremely rare. It does happen, but tuberculosis in a gland as vascular as the thyroid is rare indeed. I doubt if we have ever seen a case in this hospital, although it has been reported. I have never seen a case, and I recall a recent case at the Baker Memorial with a hard nodular mass and the signs of tuberculosis in which Dr. Donaldson operated, thinking that it was tuberculosis of the thyroid gland. They were tuberculous nodes densely adherent to the gland but not invading it. Is that correct, Dr. Donaldson?

DR. GORDON A. DONALDSON: That is my recollection.

DR. CHAPMAN: Another important point is that the mass was nontender. Tuberculous thyroiditis would produce signs of inflammation that would have been evident on physical examination.

Could this have been amyloid disease of the kidney and the thyroid gland? One must consider amyloid in the thyroid gland. I had not been aware of that diagnosis until a case was discussed at Grand Rounds a few months ago of a man with rheumatoid arthritis, who had such a mass, which histologically proved to be amyloid. One must therefore keep that possibility in mind, but another case in the same year would be a great rarity. Simply on the law of chances, I should say that it was not amyloid.

Since this man liked cabbage, which is one of the common goitrogens because of its content of cyanate ion, we come to the most likely possibility — that is, an iodine-deficiency goiter. Astwood[1] and the VanderLaans[2] have recently explained the mechanism by which this occurs. Another possibility is a type of thyroiditis known as Hashimoto struma. In some cases of the Hashimoto type giant-cell formation simulating tuberculosis has been described. If Dr. Mallory says that there were giant cells I can still say that does not prove the disease to have been tuberculosis. So much for the differential diagnostic points concerning the thyroid gland.

Then we come to the final episode. Why did this man die so abruptly? I am sure that I do not know. There are two or three things that come to mind. He was doing fairly well until he suffered the shock of rupture of the perirectal abscess. If he did not die from the shock of that, he might have had sepsis from it. He had kyphosis, the heart was enlarged, and he had premature beats, and irritability of the heart, suggesting that the myocardium was not a very healthy one. As a terminal episode he may have had severe heart failure or cardiac infarction. I see no way of making the diagnosis.

In conclusion, I shall say that he had tuberculosis, bilateral and extensive, with cavitation, perirectal abscess, questionable prostatic tuberculosis and questionable amyloid kidney with uremia, and that in my judgment this was an iodine-deficient goiter induced by goitrogens and not hyperplasia, or amyloid disease, tuberculosis or Hashimoto struma.

DR. CHARLES E. RICHARDS: I wonder why Dr. Chapman has not mentioned carcinoma in the differential diagnosis.

DR. CHAPMAN: There is no mention of the gland's being fixed. It seemed unlikely that it would be carcinoma, but I suppose that I could have included that diagnosis to be encyclopedic.

DR. DONALD S. KING: I think that he had active tuberculosis, but I wonder if one could prove it. I should have to guess that he had it, but I am not absolutely certain.

DR. TRACY B. MALLORY: I almost hesitate to admit that this patient was in the hospital for five days and that no sputum examination was ever made.

PROFESSOR HERMAN SIKL: Perhaps blockage of the bronchus produced fibrosis of the lungs.

DR. HELEN S. PITTMAN: When I first saw this man he was in the Out Patient Department, and I had no idea what was the matter basically. Obviously, he had an enormous thyroid gland — not hard or tender and not fixed, but causing some pressure. I thought that he had Pott's disease and a tuberculous draining abscess, secondary to that, and was quite sure that he had old pulmonary tuberculosis and arteriosclerotic heart disease.

DR. CHAPMAN: That is helpful, and it makes me think more of carcinoma, as Dr. Richards brought out. I thought that this was a stationary lesion. As you describe it, it makes one think of carcinoma simplex, a rapidly spreading type. The man was not very observant, and the thyroid gland seems to have been growing much faster than one would gather from the history.

DR. PITTMAN: The patient was not a careful observer, but our impression was that the gland was growing rapidly.

CLINICAL DIAGNOSES

Adenoma, nontoxic, of thyroid gland.
Tuberculosis of vertebras.
Perirectal abscess and prostatitis.

DR. CHAPMAN'S DIAGNOSES

Tuberculosis, bilateral, extensive, with cavitation.
Perirectal abscess.
Prostatic tuberculosis?
Amyloid kidney(?), with uremia.
Iodine-deficient goiter (cyanate).

ANATOMICAL DIAGNOSES

Pulmonary tuberculosis, chronic.
Bronchiectasis.
Cor pulmonale, slight.
Tuberculosis of prostate gland, seminal vesicles and epididymis, active.
Amyloid goiter.
Amyloid nephrosis, slight.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The heart did not show any coronary disease. It was slightly hypertrophied, particularly the right ventricle, justifying the diagnosis of cor pulmonale. This is not uncommon in kyphoscoliosis, but there was also severe pulmonary disease. The pulmonary picture was very complicated. There was extensive old tuberculosis, but it was mostly fibrous, with encapsulated caseous foci, and relatively inactive. The cavities that Dr. Wyman demonstrated were greatly dilated bronchi, which, at the time of autopsy, were filled with purulent secretions. I believe that bronchiectasis was perhaps the most important factor in the patient's death. The vertebral column was, of course, greatly twisted, as the x-ray films show, but there were no collapsed vertebras that would permit a diagnosis of Pott's disease. The most active tuberculosis found was in the lower urinary tract. The prostate, seminal vesicles and right epididymis all showed involvement.

Our interest naturally centers around the thyroid gland, which showed parenchymal atrophy, great numbers of fat cells and masses of homogeneous material that had the staining reactions of amyloid. This makes the second amyloid goiter in a short time. Amyloid is a rare disease in this area. These are the only 2 cases of amyloid goiter that I have seen. Perhaps Professor Sikl is more familiar with them in his material in Prague.

PROFESSOR SIKL: No.

DR. LOUIS K. DAHL: Was there any amyloid anywhere else in the body?

DR. MALLORY: Traces were present in the kidneys but not in the spleen, the liver or the adrenal glands — the other usual foci.

DR. ALLAN G. BRAILEY: Is it apparent why the patient died?

DR. MALLORY: We have no explanation why he died or when he died. Patients with scoliosis are very prone to sudden cardiac death without any warning or premonitory signs. He had, in addition, active tuberculosis and severe bronchiectasis. Perhaps, as Dr. Chapman suggests, the rupture of the perirectal abscess was enough to tip the balance.

REFERENCES

1. Astwood, E. B. Chemical nature of compounds which inhibit function of thyroid gland. *J. Pharmacol. & Exper. Therap.* **78**:79-89, 1943.
2. VanderLaan, J. E., and VanderLaan, W. P. Iodide concentrating mechanism of rat thyroid and its inhibition by thiocyanate. *Endocrinology* **40**:403-416, 1947.

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A WARNING REGARDING THE USE OF FOLIC ACID

AN alarming incidence has been reported of neurologic relapse or progression of pre-existing neurologic lesions in cases of pernicious anemia treated with folic acid, the term being used to indicate synthetic pteroylglutamic acid. Sargent's review, presented elsewhere in this issue of the *Journal*, places the incidence of such neurologic lesions at about 20 per cent during a period of one year or less of therapy. More recent studies show an even higher rate. Ross[1] observed an incidence of over 50 per cent in 21 cases. In Wagley's[2] series of 10 cases, 8 developed neurologic lesions or progression of pre-existing lesions within eight days to twelve months after the institution of folic acid therapy. Two cases of sprue have been noted in which neurologic lesions occurred during folic acid therapy.[3] In one of these cases, the lesions recurred during a second course of folic acid therapy. These figures are obviously in striking contrast to the well known results with therapy by liver extract or gastric preparations, which in adequate dosage almost invariably arrest existing neurologic lesions or prevent the subsequent development of nerve changes. Indeed, these findings suggest that substitution of the newer remedy places the patient's continued health in jeopardy.

In most of the cases treated with folic acid the patients were subjectively in good health, and the red-cell count and hemoglobin had returned to normal levels at the time that the neurologic signs appeared. Increasing the dosage of folic acid nevertheless failed to prevent progress of the neurologic lesions. These have occurred in cases receiving as much as 500 mg. daily, or about twenty-five times the average amount required for the relief of the hematologic abnormalities. It appears, therefore, that the neurologic changes cannot be ascribed to inadequate folic acid dosage.

Three possible relations of folic acid to the neurologic disturbances exist. First, folic acid may merely be allowing the disease to run its natural course so far as the nervous system is concerned. This may actually have happened in some of the reported cases. In contrast to the neurologic signs in combined system disease, however, few cases have shown unequivocal evidence of lateral column involvement, despite severe and extensive posterior column disturbance. Secondly, Heinle and Welch[4] have suggested that folic acid in relieving one deficiency accentuates another, which is in turn responsible for the neurologic changes, as occurs occasionally with other members of the vitamin B complex. Thus, cure of pellegra by nicotinic acid may result in manifest thiamine deficiency. The third explanation is that folic acid may actually exert a positively deleterious influence on the nervous system. Thus, by some close chemical relation to substances required to maintain the integrity of the nervous system, folic acid may competitively interfere with the nutrition of the spinal cord just as certain vitamin deficiencies in experimental animals may be caused by closely related chemicals.

Thiamine deficiency, for example, may be induced by the administration of pyrithiamine, and pantothenic acid deficiency by pantoyltaurine. Ross[3] has recently suggested that pteroylglutamic acid may interfere with the metabolism of glutamic acid by the central nervous system, which, according to a preliminary observation by Pearson,[5] it appears to do, at least in vitro.

A positively injurious effect of folic acid therapy is consistent with the following features of the neurologic disturbance: in many cases an explosive onset and spread of the neurologic lesion has been noted. On the other hand, whereas combined system disease may start acutely, it does so only rarely. Several cases have been reported in which liver extract had been taken sporadically and in amounts inadequate to maintain normal blood levels for periods as long as ten years, without the development of nerve lesions. Yet on changing to folic acid therapy the sudden onset of severe neurologic manifestations occurred within a few weeks.[6] Ross[1] observed 1 case in which the addition of liver-extract therapy produced little if any improvement in the neurologic picture until folic acid administration was stopped. Indeed, the usual improvement in neurologic function occurring on withdrawal of folic acid and the institution of liver-extract therapy may be ascribed as much to the removal of the causative factor as to a response to the liver extract. Thus, giving liver extract with folic acid may not guarantee that neurologic disturbances will not develop. A further suggestion of a toxic action of folic acid is that the incidence of neurologic changes during folic acid therapy appears to parallel to some extent the dosage and frequency of administration. In cases treated with large daily doses of 25 to 50 mg. the incidence has been highest, whereas in a series receiving only 75 mg. once a week, the incidence was but 1 out of 11 cases. A possible explanation is that a large portion of a single dose is lost in the urine within twenty-four hours and that consequently with weekly administration the nervous system is exposed to very little folic acid in the intervening six days.

The inadequacy of folic acid in the treatment of pernicious anemia is also noted in the incidence of glossitis with such therapy. In Hall's[7] series 7 patients showed glossitis before commencement of therapy. Three improved temporarily and then relapsed, and 1 became worse. In Wagley's[2] series, 2 patients developed glossitis for the first time while on folic acid therapy, and another showed marked increase in the soreness of the tongue and developed glossal petechiae. Such developments are virtually unknown with adequate therapy by liver or stomach preparations.

Pteroylglutamic acid is the first hematopoietic substance in pernicious anemia to be chemically identified. When it became available in pure synthetic form about two years ago, it appeared likely to replace the older empirical but highly effective preparations of liver or stomach. Now, however, sufficient evidence has accumulated to justify a warning that synthetic pteroylglutamic acid (folic acid) should not be used in the treatment of pernicious anemia. In view of the reports of folic-acid-induced neurologic lesions in sprue,[3] this restriction should probably apply also to other nutritional macrocytic anemias. Folic acid has failed to be effective in other conditions in which liver or stomach preparations have also failed to benefit the patient. Consequently the use of folic acid as a therapeutic agent appears to offer no new benefit but only risk to the patient.

References

1. Ross, J. F. Development and progression of subacute combined degeneration of spinal cord in patients with pernicious anemia treated with synthetic pteroylglutamic acid. *Blood* (in press).
2. Wagley, P. F. Neurologic disturbances with folic acid therapy. *New Eng. J. Med.* (in press).
3. Ross, J. F. Personal communication.
4. Heinle, R. W., and Welch, A. D. Folic acid in pernicious anemia: failure to prevent neurologic relapse. *J. A. M. A.* **133**:739-741, 1947.
5. Pearson, O. H. Personal communication.
6. Vilter, C. F., Vilter, R. W., and Spies, T. D. Treatment of pernicious and related anemias with synthetic folic acid. I. Observations on maintenance of normal hematologic status and on occurrence of combined system disease at end of one year. *J. Lab. & Clin. Med.* **32**:262-273, 1947.
7. Hall, B. E., and Watkins, C. H. Experience with pteroylglutamic (synthetic folic) acid in treatment of pernicious anemia. *J. Lab. & Clin. Med.* **32**:622-634, 1947.

EPIDEMIC LEAD POISONING

It is close to a century since the medical profession began to warn the public of the danger of lead poisoning. They did it poetically in those days, too; Dr. Samuel L. Dana, of Newton, told the city officials of Lowell, "It is found by experience that the young, the delicate, soonest succumb under the effects of lead drank in their daily drink, and like

the dews of heaven, descending on all, the gentlest and fairest feel the chill which soon closes in death."[1]

In recent years the public has been amply warned of the lead hazards by which it may be surrounded. Emphasis has sometimes been mistakenly placed by the medical profession, as when it warned against lead painted toys and children's cribs only to find that none of the toy or crib manufacturers used lead in their paints.[2] The vast expansion in the use of lead by modern civilization, however, makes a far wider field for exposure than that produced by painted surfaces, even including those painted with the brand that is reputed to "cover the world."

Approximately a million tons of lead are used each year in the United States. Symptoms from the absorption of this metal are now almost wholly confined to those who are exposed in industry. The largest single user of lead is the storage-battery industry, and although poisoning may and does occur in this and other industries, it is, on the whole, well controlled. In nonindustrial life it is only under peculiar and unusual circumstances that lead poisoning appears, but several epidemics, which extend back to 1933, have been recorded that seem to be difficult to approach from the point of view of public education. These epidemics were due to the use of discarded storage-battery casings for fuel. The casings burn readily but are encrusted with lead salts, which become volatilized in the smoke and fumes. When such fumes escape through a leaky stove they can readily poison a whole family. The most recent account of this sort of epidemic appeared in an article by Cooper[3] in which an outbreak in Staunton, Virginia, is described. Health authorities discovered that war-time scarcity of fuel had led a whole neighborhood into the habit of burning discarded battery casings, with the result that 17 children were found to have latent or toxic lead poisoning. It is interesting to note that Dr. Cooper agrees with Dr. Dana, quoted above, for he writes concerning one aspect of the subject, "In epidemics of lead poisoning in which both children and adults have been exposed in the same manner and amount, children are uniformly found to be more susceptible, particularly those under four years of age."

With the coming of colder weather, and with the continuation of a fuel supply that is neither abundant nor cheap, a word of warning regarding this possible source of lead poisoning may be appropriately placed in the minds of physicians, public-health officials and even legislators, for there could be a law to regulate the disposal of discarded battery casings — many less rational laws have been enacted.

References

1. Adams, H. On the action of water on lead pipes, and the diseases proceeding from it. A report to the American Medical Association, 1852.
2. Wormser, F. E. Facts and fallacies concerning exposure to lead. *Occupational Med.* **3**:135-144, 1947.
3. Cooper, G., Jr. Epidemic of inhalation lead poisoning with characteristic skeletal changes in children involved. *Am. J. Roentgenol.* **58**: 129-141, 1947.

MASSACHUSETTS MEDICAL SOCIETY

BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

APPOINTMENT OF DR. H. QUIMBY GALLUPE

Dr. H. Quimby Gallupe, of Waltham, has been appointed by the president of the Massachusetts Medical Society secretary *pro tempore* to complete the unexpired term of Dr. Joseph Garland, who resigned to assume the editorship of the *New England Journal of Medicine*. Dr. Gallupe's appointment dates from November 1, 1947, when his predecessor's resignation became effective.

Dr. Gallupe is well known to the members of the Society for the exceptional efficiency with which he has performed his duties as secretary of the Massachusetts Board of Registration in Medicine over a period of nearly six years, and for his authorship of the Gallupe Plan, first put into operation at the Waltham Hospital two years ago.

The new secretary graduated from Tufts College in 1911 and from Harvard Medical School in 1918. He is surgeon-in-chief of the Waltham Hospital. In addition to his position as secretary of the Board of Registration in Medicine he is secretary of the Board of Registration in Nursing, chairman of the Approving Authority for Medical Schools and secretary of the Approving Authority for Nursing Schools. In the Massachusetts Medical Society he has served long as councilor from the Middlesex South District and, in addition, has been chairman of the Committee on Arrangements, chairman of the Committee on Membership and Finance and supervising censor.

His broad experience should be a distinct asset to the Society.

A HUNDRED YEARS AGO

Dr. Henry J. Bigelow reports the unusual case of Jane McMurphy of Derry, New Hampshire. She is 17, small in stature, and of healthy appearance. Five years ago a piece of tobacco was inserted in her right ear by an old woman for earache. Of the piece of tobacco the patient saw no more at the time, but at the end of a month and for the subsequent months a physician succeeded in removing a portion of what was said to be tobacco, and at the end of a year two more fragments were extracted. In March 1846, the patient while lying in bed first heard a noise. It commenced suddenly and since then it has continued with little intermission. A person sitting in the room with this patient, hears a distant muffled sound, which might easily be mistaken for the rapid dropping of water into the bowl of a closed washstand. The sound may be conveyed by the words *click click click*, or occasionally *click-click*, *click-click*, etc. The patient being requested to open her mouth, the sound becomes surprisingly distinct and audible, all the beats being apparently stimulated by the effort or by the contact of the air and the ticking becomes rapid. There is no discoverable discharge of pus or blood. The sound may be in an alternate opening and closure of the moist mouth of a sac, by which a bubble of air is expelled at each contraction, and a bubble sucked in at each dilation of its cavity. Such a sac exists between the vocal cords, or might be formed at one extremity of the os hyoides, with a fistulous opening. Such a solution of the cause of this singular sound is far from satisfactory, yet it is difficult to adduce any additional evidence of its nature. During her residence in the Hospital, Dr. B. deemed it unnecessary to harass the patient by repeating applications which seemed to have been faithfully tried; and the patient was altogether unwilling to submit to the division of one of the pillars of the palate which he proposed to her. — From a recent conversation with a medical practitioner belonging to the State of Tennessee, we learned the novel fact that a decided advantage is realized by consumptive patients in the middle and southern states in going North instead of South. Here the opinion is universal that persons with irritable lungs and more especially such as have a decided tendency to phthisis should go somewhere South. Without contending with anyone on the doctrines of contraries, as going South from the North, and North from the South, to allay symptoms and tendencies similar in character, we prefer that those most familiar with the results of such practice should discuss the subject — and whatever light may be exhibited, if it is truly light, will be received by us and the profession with feelings of gratitude. — At Meredith Bridge, N. H., Mr. B. F. Palmer carries on the manufacture of artificial limbs to a degree of perfection that both astonishes and delights all who have examined his ingenious life-like looking workmanship. Should the Mexican war continue much longer, the demand upon Mr. Palmer's establishment must actively increase. — Dr. Channing, having been Dean of the Medical Faculty of Harvard College for twenty-two years, has resigned the office, and Dr. Holmes has been appointed in his place. — H. K., a farmer, aged about 45, stout and healthy, of sanguine temperament, much addicted to inebriety, and very quarrelsome while under the influence of liquor, on August 19th, 1840, while intoxicated, undertook to chastise a small man. The latter, not feeling a disposition to submit to a drubbing, shot Mr. K. with a shot-gun loaded with shot and tow wadding, the muzzle of the gun being in contact with the left side of the epigastric region. Mr. K. fell, as if dead, and was conveyed home by four men in a sheet. On medical examination there was a large opening in the left side, as broad as a man's hand and about as long; indeed it looked as if his whole side had been torn away. He was immediately given a little of his favorite beverage, to wit, brandy and water, and bottles of hot water were applied to the axillae and between the thighs. On further examination it was found that the seventh and eighth ribs had been torn off from the attachment at the sternum to within three inches of the spine; together with all their appurtenances, the pleura included — thus exposing the lungs, diaphragm, stomach and pericardium! Most of the wadding was removed, and some of the fragments of the missing ribs. In the course of time Mr. K. recovered his former health and strength; he also returned to his former habit of dissipation and has had many a pugilistic contest since. In consequence of the loss of two ribs, he leans considerably to the left side. The case presents several points of interest. Here was a man with almost half of his left side torn off, thus admitting a free current of air not only into the pleura, but lungs and whole cavity of the chest. He survived contrary to the teaching that it is death for air to penetrate through the thoracic parietes, and contrary to the aphorism of Hunter, "that those who always live above par are extremely liable to sink when attacked by disease or injury." He felt no inconvenience nor unpleasant consequences despite the presence of a silver tube which he was forced to wear for several months to drain the pleural cavity. — Extracted from the *Boston Medical and Surgical Journal*, November 1847.

R. F.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR AUGUST, 1947

Résumé

Diseases	August 1947	August 1946	Seven-Year Median
Chancroid	2	0	1*
Chicken pox	179	123	123
Diphtheria	17	20	11
Dog bite	1033	1019	1025
Dysentery, bacillary	9	1	15
German measles	41	46	46
Gonorrhea	308	365	374
Granuloma inguinale	1	0	0*
Lymphogranuloma venereum	1	0	0*
Malaria	7	21	13
Measles	125	400	296
Meningitis, meningococcal	0	4	5
Meningitis, Pfeiffer-bacillus	1	2	1
Meningitis, pneumococcal	0	0	1†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	1	0	0†
Meningitis, other forms	1	0	0†
Meningitis, undetermined	3	4	4†
Mumps	170	142	271
Pneumonia, lobar	77	29	76
Poliomyelitis	80	62	45
Salmonellosis	19	45	24
Scarlet fever	72	110	195
Syphilis	187	310	341
Tuberculosis, pulmonary	183	233	252
Tuberculosis, other forms	12	18	19
Typhoid fever	2	5	5
Undulant fever	7	6	5
Whooping cough	475	498	508

*Three-year median.

†Five-year median.

Comment

Diseases above the seven-year median are chicken pox, diphtheria, dog bite, lobar pneumonia, poliomyelitis and undulant fever.

Diseases below the seven-year median are bacillary dysentery, German measles, gonorrhea, malaria, measles, meningococcal meningitis, mumps, salmonellosis, scarlet fever, syphilis, pulmonary tuberculosis, tuberculosis (other forms), typhoid fever and whooping cough.

Diphtheria incidence is continuing the seasonal decline — 17 cases compared to 20 in July. The trend will undoubtedly reverse early in the fall.

Poliomyelitis has increased from 21 cases in July to 80 this month. The seven-year median incidence is 45. The disease will probably show an early seasonal peak in contrast to the late peak in 1946.

This is the first month in which no cases of meningococcal meningitis were reported since 1940.

Geographical Distribution of Certain Diseases

Diphtheria was reported from: Boston, 9; Canton, 1; Chelsea, 1; Medford, 2; Melrose, 1; Revere, 2; Saugus, 1; total, 17.

Dysentery, amebic, was reported from: Boston, 1; total, 1.

Dysentery, bacillary, was reported from: Beverly, 1; Boston, 2; Cambridge, 1; Gloucester, 1; Lawrence, 1; Worcester, 3; total, 9.

Lymphocytic choriomeningitis was reported from: Pittsfield, 1; total, 1.

Malaria was reported from: Boston, 3; Lynn, 2; Manchester, 1; Newton, 1; total, 7.

Meningitis, Pfeiffer-bacillus, was reported from: Worcester, 1; total, 1.

Meningitis, streptococcal, was reported from: Norwood, 1; total, 1.

Meningitis, other forms, was reported from: Brookline, 1; total, 1.

Meningitis, undetermined, was reported from: Dracut, 1; Haverhill, 1; Springfield, 1; total, 3.

Poliomyelitis was reported from: Andover, 1; Arlington, 2; Attleboro, 1; Beverly, 2; Boston, 9; Brockton, 1; Cambridge, 6; Carlisle, 2; Dighton, 1; Fairhaven, 2; Falmouth, 1; Fall River, 5; Franklin, 1; Freetown, 1; Great Barrington, 1; Hull, 1; Ipswich, 1; Lenox, 1; Lowell, 1; Lynn, 1; Middleboro, 1; Milford, 1; Milton, 1; New Bedford, 3; New Marlboro, 1; Newton, 4; North Attleboro, 2; Northampton, 1; Northfield, 1; Pittsfield, 2; Revere, 1; Salem, 3; Somerville, 2; Southbridge, 1; Stoneham, 1; Taunton, 4; Waltham, 1; West Stockbridge, 1; Weston, 1; Westwood, 2; Winthrop, 2; Worcester, 3; total, 80.

Salmonellosis was reported from: Beverly, 2; Boston, 2; Cambridge, 1; Chatham, 1; Lowell, 1; Monterey, 2; Natick, 1; New Bedford, 1; Newton, 1; Salem, 1; Taunton, 1; Waltham, 1; Watertown, 2; Winchester, 1; Worcester, 1; total, 19.

Trachoma was reported from: Boston, 1; total, 1.

Trichinosis was reported from: Boston, 1; Fall River, 1; Pittsfield, 1; Springfield, 1; Stoneham, 1; total, 5.

Tularemia was reported from: Duxbury, 1; Wareham, 1; total, 2.

Typhoid fever was reported from: Boston, 1; Grafton, 1; total, 2.

Undulant fever was reported from: Boston, 1; Chicopee, 1; Gardner, 1; Haverhill, 1; Holyoke, 1; Lexington, 1; Melrose, 1; total, 7.

MISCELLANY

NOTE

Dr. Erich Lindemann, formerly associate in psychiatry at Harvard Medical School, was recently appointed to the Harvard University Faculty of Arts and Sciences to broaden the scope of the new Department of Social Relations. He will continue as a member of the staff of Massachusetts General Hospital. Dr. Lindemann will concern himself with the study of psychologic disturbances of the individual, with special reference to the role of his social relations as a cause of disturbance and as a source of therapeutic aid. His courses will include dynamic psychology and clinical problems in psychologic medicine. In joining the Department of Social Relations, which was established last year, Dr. Lindemann will associate himself with sociologists, psychologists and anthropologists. The new Department was formed to break down the limitations of individual departments in working on common problems of social relations.

Dr. Lindemann's research has included experiments in the use of narcosynthesis in treating mental disorders and an original study of the psychiatry of grief, which followed the Cocoanut Grove fire in Boston.

Dr. Lindemann received his Ph.D. degree in Psychology from Marburg University in 1922 and his M.D. degree from Cologne University in 1926. He came to the United States in 1927. He was a research fellow at Iowa State University from 1927 to 1929, afterward serving as instructor in psychology and psychiatry (1929–1931), assistant professor of psychiatry (1931–1935), and assistant professor of psychology (1932–1935). He was research fellow in neurology and psychiatry at the Harvard Medical School from 1935 to 1937, and was instructor in psychiatry (1937–1941) and associate in psychiatry from 1941 until his present appointment. He also served as instructor in psychiatry, Harvard School of Public Health.

Hospital positions held by Dr. Lindemann include assistant psychiatrist and chief, Psychiatric Out Patient Department, Iowa Psychopathic Hospital (1931–1935), student mental-hygiene adviser (1933–1935), associate psychiatrist (1937) and psychiatrist (1943), Massachusetts General Hospital, physician-in-charge, Psychiatric Out Patient Department (1937) and consulting psychiatrist, Massachusetts Eye and Ear Infirmary (1941).

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Postnatal Development of the Human Cerebral Cortex. By J. LeRoy Conel, A.M., Ph.D., professor of anatomy, Boston University School of Medicine, and research associate in pathology, Harvard Medical School, Children's Hospital and Infants' Hospital, Boston. Volume I, 104 pp., 98 plates; Volume II, 136 pp., 108 plates; Volume III, 158 pp., 104 plates. Cambridge: Harvard University Press, 1939–1946. Volumes I and II, $8.00 each; Volume III, $12.50.

The Ranks of Death: A medical history of the conquest of America. By P. M. Ashburn, M.D. Edited by Frank D. Ashburn. 8°, cloth, 298 pp. New York: Coward-McCann, Incorporated, 1947. $5.00.

The Development of Inhalation Anesthesia: With special reference to the years 1846–1900. By Barbara M. Duncum, D.Phil. (Oxon.), member of the Nuffield Department of Anaesthetics, University of Oxford. Publications of the Wellcome Historical Museum. 8°, cloth, with 161 illustrations. New York: Oxford University Press, 1947. $12.00.

Human Genetics. By Reginald Ruggles Gates, Ph.D., D.Sc., LL.D. 8°, cloth, two volumes, 1518 pp., with 325 illustrations. New York: Macmillan Company, 1946. $15.00.

Handbook of Correctional Psychology. Edited by Robert M. Lindner, M.D., and Robert V. Seliger, M.D. 8°, cloth, 691 pp. New York: Philosophical Library, 1947. $10.00.

Rh: Its relation to congenital hemolytic disease and to intragroup transfusion reactions. By Edith L. Potter, M.D., Ph.D., assistant professor of pathology, Department of Obstetrics and Gynecology, University of Chicago, and Chicago Lying-in Hospital. 8°, cloth, 344 pp., with 65 illustrations. Chicago: Year Book Publishers, Incorporated, 1947. $5.50.

The Self You Have to Live with. By Winfred Rhoades. Revised edition. 8°, cloth, 254 pp. Philadelphia: J. B. Lippincott Company, 1947. $2.00.

Diseases of the Chest, with Emphasis on X-ray Diagnosis. By Eli H. Rubin, M.D., attending physician, Division of Pulmonary Diseases, Montefiore Hospital and County Sanatorium, New York City, and visiting physician in tuberculosis and physician-in-charge, Chest Clinic, Morrisania City Hospital, New York City. With a section, "The Principles of Surgical Treatment," by Morris Rubin, M.D., assistant visiting surgeon, Triboro Hospital and Morrisania City Hospital, New York City. 4°, cloth, 685 pp., with 355 illustrations and 24 color plates. Philadelphia: W. B. Saunders Company, 1947. $12.00.

Studies and Essays in the History of Science and Learning. Dedicated to George Sarton, on the occasion of his sixtieth birthday. Edited by M. F. Ashley Montague. 8°, cloth, 597 pp., with portrait and 38 illustrations. New York: Henry Schuman, 1947. $12.00.

Gastritis. By Rudolf Schindler, M.D., clinical professor of internal medicine (gastroenterology), College of Medical Evangelists, Los Angeles, senior member of attending staff, Los Angeles County Hospital, consultant in gastroenterology, Birmingham General Hospital, Veterans Administration, Van Nuys, California, and Cedars of Lebanon Hospital, Los Angeles. 8°, cloth, 462 pp., with 96 plates. New York: Grune and Stratton, 1947. $10.00.

Encyclopedia of Endocrinology. Section IV. *Ovary.* Volume VII (two volumes), ovarian tumors and bibliography. By Hans Selye, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada), professor and director, Institute of Experimental Medicine and Surgery, University of Montreal. 4°, cloth, 289, 427, 60 pp., with 38 plates. Montreal: Richardson, Bond and Wright, 1946. $21.75.

The Psychoanalytic Study of the Child. Volume II. 8°, cloth, 424 pp. New York: International Universities Press, 1947. $7.50.

Curare: Its history, nature and clinical use. By A. R. McIntyre, Ph.D., M.D., professor of physiology and pharmacology, University of Nebraska College of Medicine. 8°, cloth, 240 pp., with 23 illustrations. Chicago, Illinois: University of Chicago Press, 1947. $5.00.

A History of The American Medical Association 1847 to 1947. By Morris Fishbein, M.D. With Biographies of the presidents of the Association by Walter L. Bierring, M.D., and with histories of the publications, councils, bureaus and other official bodies. 4°, cloth, 1226 pp., illustrated. Philadelphia: W. B. Saunders Company, 1947. $10.00.

The Physical Background of Perception: The Waynflete lectures delivered in the College of St. Mary Magdalen, Oxford, in the Hilary Term 1946. By E. D. Adrian, O.M., F.R.S. 8°, cloth, 95 pp., with 21 illustrations. New York: Oxford University Press, 1947. $3.25.

The Development of Modern Medicine: An interpretation of the social and scientific factors involved. By Richard Harrison Shryock. 8°, cloth, 457 pp., with 9 plates. New York: Alfred A. Knopf, 1947. $5.00.

NOTICES

ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

The annual meeting of the Association of Military Surgeons of the United States will be held at the Hotel Statler, Boston, from November 13 to 15, inclusive. An unusual program is being offered, with special emphasis on many interesting features developed during the war and since V-J day. Technical information and findings not hitherto generally published will be released by high-ranking representatives of the Army, Navy and Air Force. Speakers from the United States Public Health Service and the Veterans Administration will also participate in this meeting.

All interested physicians are invited.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

A joint meeting of the Boston Society of Psychiatry and Neurology and the New England Pathological Society will be held at the Boston Medical Library, 8 Fenway, Boston, on Thursday, November 20, at 8:15. Dr. J. W. Kernohan will speak on "Secondary Changes Produced by Expanding Intracranial Lesions."

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, November 13

Friday, November 14

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

Monday, November 17

*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

Tuesday, November 18

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

Wednesday, November 19

*12:00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

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*Open to the medical profession.

(*Notices continued on page xv*)